IN THE U.S. PATENT AND TRADEMARK OFFICE

APPLICATION NUMBER : ~~487,761~~

PATENT NUMBER : 6,217,866

FILING DATE : June 7, 1995

ISSUE DATE : April 17, 2001

INVENTOR(S) : Schlessinger, et al.

Commissioner of Patents and
Trademarks
P.O. Box 1450
Alexandria VA 22313-1450

Sir:

Aventis Pharmaceuticals Inc., assignee of U.S. Patent No. 6,217,866 ("the '866 patent"), through its appointed agent, ImClone Systems Incorporated, submits this request for patent term extension for the '866 patent.

1. On February 12, 2004, the U.S. Food and Drug Administration ("FDA") approved the monoclonal antibody ("MAb") ERBITUX™ (cetuximab) for use in combination with irinotecan in the treatment of patients with Epidermal Growth Factor (EGF) Receptor (EGFR)-expressing, metastatic colorectal cancer who are refractory to irinotecan-based chemotherapy.

ERBITUX MAb is a recombinant, human/mouse chimeric, monoclonal antibody that binds specifically to the extracellular domain of the human EGFR. The MAb ERBITUX is composed of the Fv regions of a murine anti-EGFR antibody with human IgG1 heavy and kappa light chain constant regions and has an approximate molecular weight of 152 kDa. ERBITUX MAb is produced in mammalian (murine myeloma) cell culture.

The MAb ERBITUX is a sterile, clear, colorless liquid of pH 7.0 to 7.4, which may contain a small amount of easily visible, white, amorphous, cetuximab particulates. Each single-use, 50-mL vial contains 100 mg of cetuximab at a concentration of 2 mg/mL and is formulated in a preservative-free solution containing 8.48 mg/mL sodium chloride, 1.88 mg/mL sodium phosphate dibasic heptahydrate, 0.42 mg/mL sodium phosphate monobasic monohydrate, and water for Injection. A copy of the package insert is attached hereto at Tab A.

2. Regulatory review of the combination therapy involving the ERBITUX MAb and irinotecan occurred under § 351 of the Public Health Service Act.

3. The combination therapy involving ERBITUX MAb and irinotecan received permission on February 12, 2004 for commercial marketing under § 351 of the Public Health Service Act.

4. Neither ERBITUX MAb, nor the approved combination therapy with irinotecan, have been previously approved for commercial marketing or use under the Federal Food, Drug and Cosmetic Act, the Public Health Service Act, or the Virus-Serum-Toxin Act.

5. This application is submitted by the owner of the patent, Aventis Pharmaceuticals Inc., through its agent, ImClone Systems Incorporated, within the sixty (60) day period permitted for submission pursuant to 37 C.F.R. § 1.720(f). The last day that this application may be submitted is April 12, 2004. The Assignment record for name change from Rhone-Poulenc Rorer Pharmaceuticals Inc. to Aventis Pharmaceuticals Inc. is attached as Tab B. Also, the Appointment of Agent from Aventis Pharmaceuticals Inc. to ImClone Systems Incorporated is attached at Tab C.

6. The patent for which an extension is being sought is U.S. Patent No. 6,217,866, which issued April 17, 2001. The inventors listed on the face of the '866 patent are Joseph Schlessinger, David Givol, Richard Kris, George A. Ricca, Christopher Cheadle, and Victoria J. South. Under 35 U.S.C. § 154(a)(2), the '866 patent expires on April 17, 2018. A terminal disclaimer originally filed in parent Application No. 07/244,737 is being re-filed concurrently with this application and under this terminal disclaimer the '866 patent will expire on January 17, 2017.

7. A copy of the '866 patent is attached hereto at Tab D.

8. A copy of the terminal disclaimer discussed in paragraph 6 is attached hereto at Tab E. A copy of the certificate of correction that was filed on December 11, 2001, is attached hereto at Tab F. No reexamination certificates have been issued. A maintenance fee payment is not due until April 19, 2004. (See attached record of fee due dates at Tab G). Accordingly, no copy of a receipt of maintenance fee payment is available.

9. The '866 patent claims the approved combination therapy. The applicable patent claims and the manner in which each applicable claim reads on the approved product is as follows.

> Claim 1. A method for inhibiting the growth of human tumor cells that express human EGF receptors and are mitogenically stimulated by EGF, the method comprising administering an effective amount of an anti-neoplastic agent and an effective amount of a monoclonal antibody to a human cancer patient having said tumor cells; (i) wherein said antibody binds to the extra-cellular domain of the human EGF receptor of said

tumor cell; (ii) wherein the antibody is not conjugated to the anti-neoplastic agent; and (iii) wherein the antibody inhibit the binding of EGF to the EGF receptor.

ERBITUX MAb has been approved for the administration, in combination with an antineoplastic agent, to a human cancer patient having tumor cells that express human EGFR. *See, e.g.,* Package Insert at Indications and Usage. Such administration of the ERBITUX MAb is separately from, and therefore not conjugated to, the antineoplastic agent. The MAb ERBITUX binds specifically to the extra-cellular domain of the human EGFR, (*see, e.g.,* Package Insert at Description), and competitively inhibits the binding of EGFR and other ligands. *See, e.g.,* Package Insert at Clinical Pharmacology. *In vitro* assays and *in vivo* animal studies have shown that binding of the MAb ERBITUX to the EGFR results in inhibition of cell growth. *See, e.g.,* Package Insert at Clinical Pharmacology. Expression of EGFR is confirmed by immunohistochemical analysis of the tumor cells using the DakoCytomation EGFR pharmDx™ test kit. *See, e.g.,* Package Insert at EGFR Expression and Response. Moreover, the approved combination includes the anti-neoplastic agent irinotecan, which belonging to a general group of chemotherapy drugs known as topoisomerase inhibitors that stop the growth of cancer cells by preventing the development of elements necessary for cell division, and is indicated for treatment of colon and rectal cancers.

10. The relevant dates and information pursuant to 35 U.S.C. § 156(g) in order to enable the Secretary of Health and Human Services to determine the applicable regulatory review period is:

IND number: BB-IND 5804

IND effective date: 11/18/1994

BLA number: STN BL 125084/0

BLA submission date: 8/12/2003

BLA effective date: 8/14/2003

BLA approval date: 2/12/2004

11. The combination therapy of the MAb ERBITUX and irinotecan was approved by the FDA following submission of an IND and a BLA filed by ImClone Systems Incorporated. ImClone Systems Incorporated is the licensee of the '866 patent. As a brief description of the significant activities undertaken by ImClone Systems Incorporated during the applicable regulatory review period with respect to the approved product and the significant dates applicable to such activities, attached hereto at Tab H is a chronology of the communications with the FDA during the regulatory review period ending with the approval on February 12, 2004. Individual's names and proprietary information has been redacted.

12. In the opinion of the applicant, the '866 patent is eligible for patent term extension under 35 U.S.C. § 156 because:

(a) 35 U.S.C. § 156(a)

The '866 patent claims a method of using a product.

(b) 35 U.S.C. § 156(a)(1)

The term of the '866 patent has not expired before submission of this application under subsection (d)(1).

(c) 35 U.S.C. § 156(a)(2)

The term of the '866 patent has never been extended under subsection (e)(1).

(d) 35 U.S.C. § 156(a)(3)

The application for extension is submitted by Aventis Pharmaceuticals Inc., assignee of the '866 patent, through its appointed agent, ImClone Systems Incorporated, in accordance with the requirement of 35 U.S.C. § 156(d) paragraphs (1)-(4) and rules of the U.S. Patent and Trademark Office.

(e) 35 U.S.C. § 156(a)(4)
ERBITUX MAb has been subject to a regulatory review period before its commercial marketing or use.

(f) 35 U.S.C. § 156(a)(5)(A)
The commercial marketing or use of the MAb ERBITUX after the regulatory review period is the first permitted commercial marketing or use of the ERBITUX MAb, under the provision of section 351 of the Public Health Service Act under which such regulatory review period occurred.

(g) 35 U.S.C. § 156(c)(4)
No patent other than the '866 patent has been extended under subsection (e)(1) for the same regulatory review period for ERBITUX MAb.

The length of extension of the patent term of the '866 patent claimed by applicant is 391 days, until 2/12/2018. The length of the extension was determined as follows.

(a) 3,192 The number of days in the period beginning on the date an exemption under section 351 of the Public Health Service Act became effective for the approved product (11/18/1994) and ending on the date the application was initially submitted and effective for such product under section 351 of the Public Health Service Act. (8/14/03); (See 37 C.F.R. § 1.775(c)(1)).

(b) 183 The number of days in the period beginning on the date the application was initially submitted and effective for the approved product under section 351 of the Public Health Service Act, (8/14/03) and ending on the date such application was approved under such section. (2/12/04). (See 37 C.F.R. § 1.775(c)(2)).

(c) 3,375 The sum of (a) and (b). This is the regulatory review period. (37 C.F.R. § 1.775(c)).

(d) 2,343 The number of days in the regulatory review period which were on and before the '866 patent issued. (April 17, 2001). (37 C.F.R. § 1.775(d)(1)(i)).

(e) 0* The number of days in the regulatory review period during which it is determined under 35 U.S.C. § 56 (d)(2)(B) by the Secretary of Health and Human Services that applicant did not act with due diligence. (37 C.F.R. § 1.775(d)(1)(ii)).

* There has been no such determination. To the best of applicant's knowledge, ImClone Systems Incorporated was diligent during the regulatory review period.

(f) 2,343 The sum of (d) and (e).

(g) 1,032 (c)-(f). (37 C.F.R. § 1.775(d)(1)(ii)).

(h) 1,779 ½ of (a) + (b). (37 C.F.R. § 1.775(d)(1)(iii)).

(i) 1/17/2017 The original term of the '866 patent, shortened by any terminal disclaimer.

(j) 12/1/2022 The original term of the patent as shortened by any terminal disclaimer plus the number of days in (h). (37 C.F.R. § 1.775(d)(2)).

(k) 2/12/2018 The date of approval of the application under section 351 of the Public Health Service Act, or subsection (b) of section 505 or section 507 of the Federal Food, Drug, and Cosmetic Act plus 14 years. (37 C.F.R. § 1.775 (d)(3)). (2/12/2004)

(l) 2/12/2018 The earlier of (j) and (k). (37 C.F.R. § 1.775(d)(4)).

(m) 1/17/2022 (i) plus 5 years. (37 C.F.R. § 1.775 (d)(5)(i)).

(n) 2/12/2018 The earlier of (l) and (m). (37 C.F.R. § 1.775(d)(5)(ii)).

13. The applicant acknowledges a duty to disclose to the Commissioner of Patents and Trademarks and the Secretary of Health and Human Services or the Secretary of Agriculture any information which is material to the determination of entitlement to the extension sought.

14. Please charge the prescribed fee for receiving and acting upon this application for patent term extension pursuant to 37 C.F.R. § 1.20(j) to deposit account 11-0600.

15. Please address inquires and correspondence to:

Deborah A. Somerville
KENYON & KENYON
One Broadway
New York, NY 10004

16. A triplicate of these application papers is submitted herewith.

17. The following declaration of Deborah A. Somerville of Kenyon & Kenyon, is submitted herewith in compliance with the requirements of 37 C.F.R. § 1.740(b).

DECLARATION

The undersigned, Attorney for the Applicant's agent, ImClone Systems Incorporated, in compliance with 37 C.F.R. §1.740 (b)(1) (see Tab I for Power of Attorney to Deborah A. Somerville from ImClone Systems Incorporated), hereby declares as follows:

1. I am a patent attorney authorized to practice before the United States Patent and Trademark Office (Reg. No. 31,995) and I am authorized to represent ImClone Systems Incorporated in this application for patent term extension of the 6,217,866 patent and to transact all business in the United States patent and Trademark Office in connection therewith;

2. I have reviewed and understand the contents of this application for patent term extension of U.S. Patent No. 6,217,866 ("the '866 patent");

3. I believe that the '866 patent is subject to patent term extension pursuant to provisions of 37 C.F.R. § 1.710;

4. I believe that the extension of the length claimed in this application for patent term extension of the '866 patent is justified under 35 U.S.C § 156 and the applicable regulations relating thereto; and

5. I believe that the '866 patent, which is the subject of this application for patent term extension, meets the conditions for patent term extension as set forth in 37 C.F.R. § 1.720.

Respectfully submitted,

Dated: 4/8/04

Deborah Somerville/TAL
Deborah A. Somerville, Reg. No. 31,995

Attorney for Applicant's Agent
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ERBITUX™ (Cetuximab)

℞ ONLY

For intravenous use only.

WARNING

Infusion Reactions: Severe infusion reactions occurred with the administration of ERBITUX in approximately 3% of patients, rarely with fatal outcome (<1 in 1000). Approximately 90% of severe infusion reactions were associated with the first infusion of ERBITUX. Severe infusion reactions are characterized by rapid onset of airway obstruction (bronchospasm, stridor, hoarseness), urticaria, and hypotension (see **WARNINGS** and **ADVERSE REACTIONS**). Severe infusion reactions require immediate interruption of the ERBITUX infusion and permanent discontinuation from further treatment. (See **WARNINGS: Infusion Reactions** and **DOSAGE AND ADMINISTRATION: Dose Modifications.**)

DESCRIPTION

ERBITUX™ (Cetuximab) is a recombinant, human/mouse chimeric monoclonal antibody that binds specifically to the extracellular domain of the human epidermal growth factor receptor (EGFR). ERBITUX is composed of the Fv regions of a murine anti-EGFR antibody with human IgG1 heavy and kappa light chain constant regions and has an approximate molecular weight of 152 kDa. ERBITUX is produced in mammalian (murine myeloma) cell culture.

ERBITUX is a sterile, clear, colorless liquid of pH 7.0 to 7.4, which may contain a small amount of easily visible, white, amorphous, Cetuximab particulates. Each single-use, 50-mL vial contains 100 mg of Cetuximab at a concentration of 2 mg/mL and is formulated in a preservative-free solution containing 8.48 mg/mL sodium chloride, 1.88 mg/mL sodium phosphate dibasic heptahydrate, 0.42 mg/mL sodium phosphate monobasic monohydrate, and Water for Injection, USP.

CLINICAL PHARMACOLOGY

General

ERBITUX binds specifically to the epidermal growth factor receptor (EGFR, HER1, c-ErbB-1) on both normal and tumor cells, and competitively inhibits the binding of epidermal growth factor (EGF) and other ligands, such as transforming growth factor–alpha. Binding of ERBITUX to the EGFR blocks phosphorylation and activation of receptor-associated kinases, resulting in inhibition of cell growth, induction of apoptosis, and decreased matrix metalloproteinase and vascular endothelial growth factor production. The EGFR is a transmembrane glycoprotein that is a member of a subfamily of type I receptor tyrosine kinases including EGFR (HER1), HER2, HER3, and HER4. The EGFR is constitutively expressed in many normal epithelial tissues, including the skin and hair follicle. Over-expression of EGFR is also detected in many human cancers including those of the colon and rectum.

In vitro assays and *in vivo* animal studies have shown that ERBITUX inhibits the growth and survival of tumor cells that over-express the EGFR. No anti-tumor effects of ERBITUX were observed in human tumor xenografts lacking EGFR expression. The addition of ERBITUX to irinotecan or irinotecan plus 5-fluorouracil in animal studies resulted in an increase in anti-tumor effects compared to chemotherapy alone.

Human Pharmacokinetics

ERBITUX administered as monotherapy or in combination with concomitant chemotherapy or radiotherapy exhibits nonlinear pharmacokinetics. The area under the concentration time curve (AUC) increased in a greater than dose proportional manner as the dose increased from 20 to 400 mg/m². ERBITUX clearance (CL) decreased from 0.08 to 0.02 L/h/m² as the dose increased from 20 to 200 mg/m², and at doses >200 mg/m², it appeared to plateau. The volume of the distribution (Vd) for ERBITUX appeared to be independent of dose and approximated the vascular space of 2-3 L/m².

Following a 2-hour infusion of 400 mg/m² of ERBITUX, the maximum mean serum concentration (C_{max}) was 184 μg/mL (range: 92-327 μg/mL) and the mean elimination half-life was 97 hours (range 41-213 hours). A 1-hour infusion of 250 mg/m² produced a mean C_{max} of 140 μg/mL (range 120-170 μg/mL). Following the recommended dose regimen (400 mg/m² initial dose/250 mg/m² weekly dose), ERBITUX concentrations reached steady-state levels by the third weekly infusion with mean peak and trough concentrations across studies ranging from 168 to 235 and 41 to 85 μg/mL, respectively. The mean half-life was 114 hours (range 75-188 hours).

Special Populations

A population pharmacokinetic analysis was performed to explore the potential effects of selected covariates including race, gender, age, and hepatic and renal function on ERBITUX pharmacokinetics.

Female patients had a 25% lower intrinsic ERBITUX clearance than male patients. Similar efficacy and safety were observed for female and male patients in the clinical trials; therefore, dose modification based on gender is not necessary. None of the other covariates explored appeared to have an impact on ERBITUX pharmacokinetics.

ERBITUX has not been studied in pediatric populations.

CLINICAL STUDIES

The efficacy and safety of ERBITUX alone or in combination with irinotecan were studied in a randomized, controlled trial (329 patients) and in combination with irinotecan in an open-label, single-arm trial (138 patients). ERBITUX was further evaluated as a single agent in a third clinical trial (57 patients). Safety data from 111 patients treated with single-agent ERBITUX was also evaluated. All trials studied patients with EGFR-expressing metastatic colorectal cancer, whose disease had progressed after receiving an irinotecan-containing regimen.

Randomized, Controlled Trial

A multicenter, randomized, controlled clinical trial was conducted in 329 patients randomized to receive either ERBITUX plus irinotecan (218 patients) or ERBITUX monotherapy (111 patients). In both arms of the study, ERBITUX was administered as a 400 mg/m² initial dose, followed by 250 mg/m² weekly until disease progression or unacceptable toxicity. All patients received a 20-mg test dose on Day 1. In the ERBITUX plus irinotecan arm, irinotecan was added to ERBITUX using the same dose and schedule for irinotecan as the patient had previously failed. Acceptable irinotecan schedules were 350 mg/m² every 3 weeks, 180 mg/m² every 2 weeks, or 125 mg/m² weekly times four doses every 6 weeks. An Independent Radiographic Review Committee (IRC), blinded to the treatment arms, assessed both the progression on prior irinotecan and the response to protocol treatment for all patients.

Of the 329 randomized patients, 206 (63%) were male. The median age was 59 years (range 26-84), and the majority was Caucasian (323, 98%). Eighty-eight percent of patients had baseline Karnofsky Performance Status ≥80. Fifty-eight percent of patients had colon cancer and 40% rectal cancer. Approximately two-thirds (63%) of patients had previously failed oxaliplatin treatment.

The efficacy of ERBITUX plus irinotecan or ERBITUX monotherapy was evaluated in all randomized patients.

Analyses were also conducted in two pre-specified subpopulations: irinotecan refractory and irinotecan and oxaliplatin failures. The irinotecan refractory population was defined as randomized patients who had received at least two cycles of irinotecan-based chemotherapy prior to treatment with ERBITUX, and had independent confirmation of disease progression within 30 days of completion of the last cycle of irinotecan-based chemotherapy.

The irinotecan and oxaliplatin failure population was defined as irinotecan refractory patients who had previously been treated with and failed an oxaliplatin-containing regimen.

The objective response rates (ORR) in these populations are presented in Table 1.

Table 1: Objective Response Rates per Independent Review

	ERBITUX + Irinotecan		ERBITUX Monotherapy		Difference (95% CI[a])	
Populations	**n**	**ORR (%)**	**n**	**ORR (%)**	**%**	**p-value CMH[b]**
All Patients	218	22.9	111	10.8	12.1 (4.1 - 20.2)	0.007
• Irinotecan-Oxaliplatin Failure	80	23.8	44	11.4	12.4 (-0.8 - 25.6)	0.09
• Irinotecan Refractory	132	25.8	69	14.5	11.3 (0.1 - 22.4)	0.07

[a] 95% confidence interval for the difference in objective response rates.
[b] Cochran-Mantel-Haenszel test.

The median duration of response in the overall population was 5.7 months in the combination arm and 4.2 months in the monotherapy arm. Compared with patients randomized to ERBITUX alone, patients randomized to ERBITUX and irinotecan experienced a significantly longer median time to disease progression (see Table 2).

Table 2: Time to Progression per Independent Review

Populations	ERBITUX + Irinotecan (median)	ERBITUX Monotherapy (median)	Hazard Ratio (95% CI[a])	Log-rank p-value
All Patients	4.1 mo	1.5 mo	0.54 (0.42 - 0.71)	<0.001
• Irinotecan-Oxaliplatin Failure	2.9 mo	1.5 mo	0.48 (0.31 - 0.72)	<0.001
• Irinotecan Refractory	4.0 mo	1.5 mo	0.52 (0.37 - 0.73)	<0.001

[a] Hazard ratio of ERBITUX + irinotecan: ERBITUX monotherapy with 95% confidence interval.

Single-Arm Trials

ERBITUX, in combination with irinotecan, was studied in a single-arm, multicenter, open-label clinical trial in 138 patients with EGFR-expressing metastatic colorectal cancer who had progressed following an irinotecan-containing regimen. Patients received a 20-mg test dose of ERBITUX on day 1, followed by a 400-mg/m² initial dose, and 250 mg/m² weekly until disease progression or unacceptable toxicity. Patients received the same dose and schedule for irinotecan as the patient had previously failed. Acceptable irinotecan schedules were 350 mg/m² every 3 weeks or 125 mg/m² weekly times four doses every 6 weeks. Of 138 patients enrolled, 74 patients had documented progression to irinotecan as determined by an IRC. The overall response rate was 15% for the overall population and 12% for the irinotecan-failure population. The median durations of response were 6.5 and 6.7 months, respectively.

ERBITUX was studied as a single agent in a multicenter, open-label, single-arm clinical trial in patients with EGFR-expressing metastatic colorectal cancer who progressed following an irinotecan-containing regimen. Of 57 patients enrolled, 28 patients had documented progression to irinotecan. The overall response rate was 9% for the all-treated group and 14% for the irinotecan-failure group. The median times to progression were 1.4 and 1.3 months, respectively. The median duration of response was 4.2 months for both groups.

EGFR Expression and Response

Patients enrolled in the clinical studies were required to have immunohistochemical evidence of positive EGFR expression. Primary tumor or tumor from a metastatic site was tested with the DakoCytomation EGFR pharmDx™ test kit. Specimens were scored based on the percentage of cells expressing EGFR and intensity (barely/faint, weak to moderate, and strong). Response rate did not correlate with either the percentage of positive cells or the intensity of EGFR expression.

INDICATIONS AND USAGE

ERBITUX, used in combination with irinotecan, is indicated for the treatment of EGFR-expressing, metastatic colorectal carcinoma in patients who are refractory to irinotecan-based chemotherapy.

ERBITUX (Cetuximab) administered as a single agent is indicated for the treatment of EGFR-expressing, metastatic colorectal carcinoma in patients who are intolerant to irinotecan-based chemotherapy.

The effectiveness of ERBITUX is based on objective response rates (see **CLINICAL STUDIES**). Currently, no data are available that demonstrate an improvement in disease-related symptoms or increased survival with ERBITUX.

CONTRAINDICATIONS

None.

WARNINGS

Infusion Reactions (See BOXED WARNING: Infusion Reactions, ADVERSE REACTIONS: Infusion Reactions, and DOSAGE AND ADMINISTRATION: Dose Modifications.)

Severe infusion reactions occurred with the administration of ERBITUX in approximately 3% (17/633) of patients, rarely with fatal outcome (<1 in 1000). Approximately 90% of severe infusion reactions were associated with the first infusion of ERBITUX despite the use of prophylactic antihistamines. These reactions were characterized by the rapid onset of airway obstruction (bronchospasm, stridor, hoarseness), urticaria, and/or hypotension. Caution must be exercised with every ERBITUX infusion, as there were patients who experienced their first severe infusion reaction during later infusions.

Severe infusion reactions require the immediate interruption of ERBITUX therapy and permanent discontinuation from further treatment. Appropriate medical therapy including epinephrine, corticosteroids, intravenous antihistamines, bronchodilators, and oxygen should be available for use in the treatment of such reactions. Patients should be carefully observed until the complete resolution of all signs and symptoms.

In clinical trials, mild to moderate infusion reactions were managed by slowing the infusion rate of ERBITUX and by continued use of antihistamine medications (eg, diphenhydramine) in subsequent doses (see **DOSAGE AND ADMINISTRATION: Dose Modifications**).

Pulmonary Toxicity

Interstitial lung disease (ILD) was reported in 3 of 633 (<0.5%) patients with advanced colorectal cancer receiving ERBITUX. Interstitial pneumonitis with non-cardiogenic pulmonary edema resulting in death was reported in one case. Two patients had pre-existing fibrotic lung disease and experienced an acute exacerbation of their disease while receiving ERBITUX in combination with irinotecan. In the clinical investigational program, an additional case of interstitial pneumonitis was reported in a patient with head and neck cancer treated with ERBITUX and cisplatin. The onset of symptoms occurred between the fourth and eleventh doses of treatment in all reported cases.

In the event of acute onset or worsening pulmonary symptoms, ERBITUX therapy should be interrupted and a prompt investigation of these symptoms should occur. If ILD is confirmed, ERBITUX should be discontinued and the patient should be treated appropriately.

Dermatologic Toxicity (See ADVERSE REACTIONS: Dermatologic Toxicity and DOSAGE AND ADMINISTRATION: Dose Modifications.)

In cynomolgus monkeys, ERBITUX, when administered at doses of approximately 0.4 to 4 times the weekly human exposure (based on total body surface area), resulted in dermatologic findings, including inflammation at the injection site and desquamation of the external integument. At the highest dose level, the epithelial mucosa of the nasal passage, esophagus, and tongue were similarly affected, and degenerative changes in the renal tubular epithelium occurred. Deaths due to sepsis were observed in 50% (5/10) of the animals at the highest dose level beginning after approximately 13 weeks of treatment.

In clinical studies of ERBITUX, dermatologic toxicities, including acneform rash, skin drying and fissuring, and inflammatory and infectious sequelae (eg, blepharitis, cheilitis, cellulitis, cyst) were reported. In patients with advanced colorectal cancer, acneform rash was reported in 88% (560/633) of all treated patients, and was severe (Grade 3 or 4) in 12% (79/633) of these patients. Subsequent to the development of severe dermatologic toxicities, complications including *S. aureus* sepsis and abscesses requiring incision and drainage were reported.

Patients developing dermatologic toxicities while receiving ERBITUX should be monitored for the development of inflammatory or infectious sequelae, and appropriate treatment of these symptoms initiated. Dose modifications of any future ERBITUX infusions should be instituted in case of severe acneform rash (see **DOSAGE AND ADMINISTRATION**, Table 4). Treatment with topical and/or oral antibiotics should be considered; topical corticosteroids are not recommended.

PRECAUTIONS

General

ERBITUX therapy should be used with caution in patients with known hypersensitivity to Cetuximab, murine proteins, or any component of this product.

It is recommended that patients wear sunscreen and hats and limit sun exposure while receiving ERBITUX as sunlight can exacerbate any skin reactions that may occur.

EGF Receptor Testing

Patients enrolled in the clinical studies were required to have immunohistochemical evidence of positive EGFR expression using the DakoCytomation EGFR pharmDx™ test kit. Assessment for EGFR expression should be performed by laboratories with demonstrated proficiency in the specific technology being utilized. Improper assay performance, including use of suboptimally fixed tissue, failure to utilize specified reagents, deviation from specific assay instructions, and failure to include appropriate controls for assay validation, can lead to unreliable results. Refer to the DakoCytomation test kit package insert for full instructions on assay performance. (See **CLINICAL STUDIES: EGFR Expression and Response.**)

Drug Interactions

A drug interaction study was performed in which ERBITUX was administered in combination with irinotecan. There was no evidence of any pharmacokinetic interactions between ERBITUX and irinotecan.

Immunogenicity

As with all therapeutic proteins, there is potential for immunogenicity. Potential immunogenic responses to ERBITUX were assessed using either a double antigen radiometric assay or an enzyme-linked immunosorbant assay. Due to limitations in assay performance and sampling timing, the incidence of antibody development in patients receiving ERBITUX has not been adequately determined. The incidence of antibodies to ERBITUX was measured by collecting and analyzing serum pre-study, prior to selected infusions and during treatment follow-up. Patients were considered evaluable if they had a negative pre-treatment sample and a post-treatment sample. Non-neutralizing anti-ERBITUX antibodies were detected in 5% (28 of 530) of evaluable patients. In patients positive for anti-ERBITUX antibody, the median time to onset was 44 days (range 8-281 days). Although the number of sero-positive patients is limited, there does not appear to be any relationship between the appearance of antibodies to ERBITUX and the safety or antitumor activity of the molecule.

The observed incidence of anti-ERBITUX antibody responses may be influenced by the low sensitivity of available assays, inadequate to reliably detect lower antibody titers. Other factors which might influence the incidence of anti-ERBITUX antibody response include sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies to ERBITUX with the incidence of antibodies to other products may be misleading.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Long-term animal studies have not been performed to test ERBITUX for carcinogenic potential. No mutagenic or clastogenic potential of ERBITUX was observed in the *Salmonella-Escherichia coli* (Ames) assay or in the *in vivo* rat micronucleus test. A 39-week toxicity study in cynomolgus monkeys receiving 0.4 to 4 times the human dose of ERBITUX (based on total body surface area) revealed a tendency for impairment of menstrual cycling in treated female monkeys, including increased incidences of irregularity or absence of cycles, when compared to control animals, and beginning from week 25 of treatment and continuing through the 6-week recovery period. Serum testosterone levels and analysis of sperm counts, viability, and motility were not remarkably different between ERBITUX-treated and control male monkeys. It is not known if ERBITUX can impair fertility in humans.

Pregnancy Category C
Animal reproduction studies have not been conducted with ERBITUX. However, the EGFR has been implicated in the control of prenatal development and may be essential for normal organogenesis, proliferation, and differentiation in the developing embryo. In addition, human IgG1 is known to cross the placental barrier; therefore ERBITUX has the potential to be transmitted from the mother to the developing fetus. It is not known whether ERBITUX can cause fetal harm when administered to a pregnant woman or whether ERBITUX can affect reproductive capacity. There are no adequate and well-controlled studies of ERBITUX in pregnant women. ERBITUX should only be given to a pregnant woman, or any woman not employing adequate contraception if the potential benefit justifies the potential risk to the fetus. All patients should be counseled regarding the potential risk of ERBITUX treatment to the developing fetus prior to initiation of therapy. If the patient becomes pregnant while receiving this drug, she should be apprised of the potential hazard to the fetus and/or the potential risk for loss of the pregnancy.

Nursing Mothers
It is not known whether ERBITUX (Cetuximab) is secreted in human milk. Because human IgG1 is secreted in human milk, the potential for absorption and harm to the infant after ingestion is unknown. Based on the mean half-life of ERBITUX after multiple dosing of 114 hours [range 75-188 hours] (see **CLINICAL PHARMACOLOGY: Human Pharmacokinetics**), women should be advised to discontinue nursing during treatment with ERBITUX and for 60 days following the last dose of ERBITUX.

Pediatric Use
The safety and effectiveness of ERBITUX in pediatric patients have not been established.

Geriatric Use
Of the 633 patients who received ERBITUX with irinotecan or ERBITUX monotherapy in four advanced colorectal cancer studies, 206 patients (33%) were 65 years of age or older. No overall differences in safety or efficacy were observed between these patients and younger patients.

ADVERSE REACTIONS
Except where indicated, the data described below reflect exposure to ERBITUX in 633 patients with advanced metastatic colorectal cancer. ERBITUX was studied in combination with irinotecan (n=354) or as monotherapy (n=279). Patients receiving ERBITUX plus irinotecan received a median of 12 doses (with 88/354 [25%] treated for over 6 months), and patients receiving ERBITUX monotherapy received a median of 7 doses (with 26/279 [9%] treated for over 6 months). The population had a median age of 59 and was 60% male and 91% Caucasian. The range of dosing for patients receiving ERBITUX plus irinotecan was 1-84 infusions, and the range of dosing for patients receiving ERBITUX monotherapy was 1-63 infusions.

The most **serious adverse reactions** associated with ERBITUX were:
- Infusion reaction (3%) (see **BOXED WARNING, WARNINGS,** and **DOSAGE AND ADMINISTRATION: Dose Modifications**);
- Dermatologic toxicity (1%) (see **WARNINGS** and **DOSAGE AND ADMINISTRATION: Dose Modifications**);
- Interstitial lung disease (0.5%) (see **WARNINGS**);
- Fever (5%);
- Sepsis (3%);
- Kidney failure (2%);
- Pulmonary embolus (1%);
- Dehydration (5%) in patients receiving ERBITUX plus irinotecan, 2% in patients receiving ERBITUX monotherapy;
- Diarrhea (6%) in patients receiving ERBITUX plus irinotecan, 0% in patients receiving ERBITUX monotherapy.

Thirty-seven (10%) patients receiving ERBITUX plus irinotecan and 14 (5%) patients receiving ERBITUX monotherapy discontinued treatment primarily because of adverse events.

The most common adverse events seen in 354 patients receiving ERBITUX plus irinotecan were acneform rash (88%), asthenia/malaise (73%), diarrhea (72%), nausea (55%), abdominal pain (45%), and vomiting (41%).

The most common adverse events seen in 279 patients receiving ERBITUX monotherapy were acneform rash (90%), asthenia/malaise (49%), fever (33%), nausea (29%), constipation (28%), and diarrhea (28%).

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice. The adverse reaction information from clinical trials does, however, provide a basis for identifying the adverse events that appear to be related to drug use and for approximating rates.

Data in patients with advanced colorectal carcinoma in Table 3 are based on the experience of 354 patients treated with ERBITUX plus irinotecan and 279 patients treated with ERBITUX monotherapy.

Table 3: Incidence of Adverse Events (≥10%) in Patients with Advanced Colorectal Carcinoma

	ERBITUX plus Irinotecan (n=354)		ERBITUX Monotherapy (n=279)	
Body System	Grades 1 - 4	Grades 3 and 4	Grades 1 - 4	Grades 3 and 4
Preferred Term[1]	% of Patients			
Body as a Whole				
Asthenia/Malaise[2]	73	16	49	10
Abdominal Pain	45	8	25	7
Fever[3]	34	4	33	0
Pain	23	6	19	5
Infusion Reaction[4]	19	3	25	2
Infection	16	1	11	1
Back Pain	16	3	11	3
Headache	14	2	25	3
Digestive				
Diarrhea	72	22	28	2
Nausea	55	6	29	2
Vomiting	41	7	25	3
Anorexia	36	4	25	3
Constipation	30	2	28	1
Stomatitis	26	2	11	<1
Dyspepsia	14	0	7	0
Hematic/Lymphatic				
Leukopenia	25	17	1	0
Anemia	16	5	10	4
Metabolic/Nutritional				
Weight Loss	21	0	9	1
Peripheral Edema	16	1	10	<1
Dehydration	15	6	9	2
Nervous				
Insomnia	12	0	10	<1
Depression	10	0	9	0
Respiratory				
Dyspnea[3]	23	2	20	7
Cough Increased	20	0	10	1
Skin/Appendages				
Acneform Rash[5]	88	14	90	10
Alopecia	21	0	5	0
Skin Disorder	15	1	5	0
Nail Disorder	12	<1	16	<1
Pruritus	10	1	10	<1
Conjunctivitis	14	1	7	<1

[1] Adverse events that occurred (toxicity Grades 1 through 4) in ≥10% of patients with refractory colorectal carcinoma treated with ERBITUX plus irinotecan or in ≥10% of patients with refractory colorectal carcinoma treated with ERBITUX monotherapy.
[2] Asthenia/malaise is defined as any event described as "asthenia", "malaise", or "somnolence".
[3] Includes cases reported as infusion reaction.
[4] Infusion reaction is defined as any event described at any time during the clinical study as "allergic reaction" or "anaphylactoid reaction", or any event occurring on the first day of dosing described as "allergic reaction", "anaphylactoid reaction", "fever", "chills", "chills and fever", or "dyspnea".
[5] Acneform rash is defined as any event described as "acne", "rash", "maculopapular rash", "pustular rash", "dry skin", or "exfoliative dermatitis".

Infusion Reactions (see BOXED WARNING: Infusion Reactions)
In clinical trials, severe, potentially fatal infusion reactions were reported. These events include the rapid onset of airway obstruction (bronchospasm, stridor, hoarseness), urticaria, and/or hypotension. In studies in advanced colorectal cancer, severe infusion reactions were observed in 3% of patients receiving ERBITUX plus irinotecan and 2% of patients receiving ERBITUX monotherapy. Grade 1 and 2 infusion reactions, including chills, fever, and dyspnea usually occurring on the first day of initial dosing, were observed in 16% of patients receiving ERBITUX plus irinotecan and 23% of patients receiving ERBITUX monotherapy. (See **WARNINGS: Infusion Reactions** and **DOSAGE AND ADMINISTRATION: Dose Modifications.**)

In the clinical studies described above, a 20-mg test dose was administered intravenously over 10 minutes prior to the loading dose to all patients. The test dose did not reliably identify patients at risk for severe allergic reactions.

Dermatologic Toxicity and Related Disorders
Non-suppurative acneform rash described as "acne", "rash", "maculopapular rash", "pustular rash", "dry skin", or "exfoliative dermatitis" was observed in patients receiving ERBITUX (Cetuximab) plus irinotecan or ERBITUX monotherapy. One or more of the dermatological adverse events were reported in 88% (14% Grade 3) of patients receiving ERBITUX plus irinotecan and in 90% (10% Grade 3) of patients receiving ERBITUX monotherapy. Acneform rash most commonly occurred on the face, upper chest, and back, but could extend to the extremities and was characterized by multiple follicular- or pustular-appearing lesions. Skin drying and fissuring were common in some instances, and were associated with inflammatory and infectious sequelae (eg, blepharitis, cellulitis, cyst). Two cases of *S. aureus* sepsis were reported. The onset of acneform rash was generally within the first two weeks of therapy. Although in a majority of the patients the event resolved following cessation of treatment, in nearly half of the cases, the event continued beyond 28 days. (See **WARNINGS: Dermatologic Toxicity** and **DOSAGE AND ADMINISTRATION: Dose Modifications.**)

A related nail disorder, occurring in 14% of patients (0.3% Grade 3), was characterized as a paronychial inflammation with associated swelling of the lateral nail folds of the toes and fingers, with the great toes and thumbs as the most commonly affected digits.

Use with Radiation Therapy
In a study of 21 patients with locally advanced squamous cell cancer of the head and neck, patients treated with ERBITUX, cisplatin, and radiation had a 95% incidence of rash (19% Grade 3). The incidence and severity of cutaneous reactions with combined modality therapy appears to be additive, particularly within the radiation port. The addition of radiation to ERBITUX therapy in patients with colorectal cancer should be done with appropriate caution.

OVERDOSAGE
Single doses of ERBITUX higher than 500 mg/m² have not been tested. There is no experience with overdosage in human clinical trials.

DOSAGE AND ADMINISTRATION
The recommended dose of ERBITUX, in combination with irinotecan or as monotherapy, is 400 mg/m² as an initial loading dose (first infusion) administered as a 120-minute IV infusion (maximum infusion rate 5 mL/min). The recommended weekly maintenance dose (all other infusions) is 250 mg/m² infused over 60 minutes (maximum infusion rate 5 mL/min). Premedication with an H_1 antagonist (eg, 50 mg of diphenhydramine IV) is recommended. Appropriate medical resources for the treatment of severe infusion reactions should be available during ERBITUX infusions. (See **WARNINGS: Infusion Reactions.**)

Dose Modifications
Infusion Reactions
If the patient experiences a mild or moderate (Grade 1 or 2) infusion reaction, the infusion rate should be permanently reduced by 50%.

ERBITUX should be immediately and permanently discontinued in patients who experience severe (Grade 3 or 4) infusion reactions. (See **WARNINGS** and **ADVERSE REACTIONS.**)

Dermatologic Toxicity and Related Disorders
If a patient experiences severe acneform rash, ERBITUX treatment adjustments should be made according to Table 4. In patients with mild and moderate skin toxicity, treatment should continue without dose modification. (See **WARNINGS** and **ADVERSE REACTIONS.**)

Table 4: ERBITUX Dose Modification Guidelines

Severe Acneform Rash	ERBITUX	Outcome	ERBITUX Dose Modification
1st occurrence	Delay infusion 1 to 2 weeks	Improvement No Improvement	Continue at 250 mg/m² Discontinue ERBITUX
2nd occurrence	Delay infusion 1 to 2 weeks	Improvement No Improvement	Reduce dose to 200 mg/m² Discontinue ERBITUX
3rd occurrence	Delay infusion 1 to 2 weeks	Improvement No Improvement	Reduce dose to 150 mg/m² Discontinue ERBITUX
4th occurrence	Discontinue ERBITUX		

Preparation for Administration
DO NOT ADMINISTER ERBITUX AS AN IV PUSH OR BOLUS.

ERBITUX must be administered with the use of a low protein binding 0.22-micrometer in-line filter.

ERBITUX is supplied as a 50-mL, single-use vial containing 100 mg of Cetuximab at a concentration of 2 mg/mL in phosphate buffered saline. The solution should be clear and colorless and may contain a small amount of easily visible, white, amorphous, Cetuximab particulates. **DO NOT SHAKE OR DILUTE.**

ERBITUX CAN BE ADMINISTERED VIA INFUSION PUMP OR SYRINGE PUMP.

Infusion Pump:
- Draw up the volume of a vial using a sterile syringe attached to an appropriate needle (a vented spike or other appropriate transfer device may be used).
- Fill ERBITUX into a sterile evacuated container or bag such as glass containers, polyolefin bags (eg, Baxter Intravia), ethylene vinyl acetate bags (eg, Baxter Clintec), DEHP plasticized PVC bags (eg, Abbott Lifecare), or PVC bags.
- Repeat procedure until the calculated volume has been put into the container. Use a new needle for each vial.
- Administer through a low protein binding 0.22-micrometer in-line filter (placed as proximal to the patient as practical).
- Affix the infusion line and prime it with ERBITUX before starting the infusion.
- Maximum infusion rate should not exceed 5 mL/min.
- Use 0.9% saline solution to flush line at the end of infusion.

Syringe Pump:
- Draw up the volume of a vial using a sterile syringe attached to an appropriate needle (a vented spike may be used).
- Place the syringe into the syringe driver of a syringe pump and set the rate.
- Administer through a low protein binding 0.22-micrometer in-line filter rated for syringe pump use (placed as proximal to the patient as practical).
- Connect up the infusion line and start the infusion after priming the line with ERBITUX.
- Repeat procedure until the calculated volume has been infused.
- Use a new needle and filter for each vial.
- Maximum infusion rate should not exceed 5 mL/min.
- Use 0.9% saline solution to flush line at the end of infusion.

ERBITUX should be piggybacked to the patient's infusion line.
Following the ERBITUX infusion, a 1-hour observation period is recommended.

HOW SUPPLIED
ERBITUX™ (Cetuximab) is supplied as a single-use, 50-mL vial containing 100 mg of Cetuximab as a sterile, preservative-free, injectable liquid. Each carton contains one ERBITUX vial (NDC 66733-948-23).

Stability and Storage
Store vials under refrigeration at 2° C to 8° C (36° F to 46° F). **DO NOT FREEZE.** Increased particulate formation may occur at temperatures at or below 0° C. This product contains no preservatives. Preparations of ERBITUX in infusion containers are chemically and physically stable for up to 12 hours at 2° C to 8° C (36° F to 46° F) and up to 8 hours at controlled room temperature (20° C to 25° C; 68° F to 77° F). Discard any remaining solution in the infusion container after 8 hours at controlled room temperature or after 12 hours at 2° to 8° C. Discard any unused portion of the vial.

US Patent No. 6,217,866

ERBITUX™ is a trademark of ImClone Systems Incorporated.
Manufactured by ImClone Systems Incorporated, Branchburg, NJ 08876
Distributed and Marketed by Bristol-Myers Squibb Company, Princeton, NJ 08543

ImClone Systems Incorporated Bristol-Myers Squibb Company

ER-B0001-02-04 Issued February 2004
Based on 51-022606-00, 1169848

B

Patent Assignment Abstract of Title

NOTE:Results display only for issued patents and published applications. For pending or abandoned applications please consult USPTO staff.

Total Assignments: 1

Patent #: 6217866 **Issue Dt:** 04/17/2001 **Application #:** 08487761 **Filing Dt:** 06/07/1995

Inventors: JOSEPH SCHLESSINGER, DAVID GIVOL, FRANCOISE BELLOT, RICHARD KRIS, GEORGE A. RICCA et al

Title: MONOCLONAL ANTIBODIES SPECIFIC TO HUMAN EPIDERMAL GROWTH FACTOR RECEPTOR AND THERAPEUTIC METHODS EMPLOYING SAME

Assignment: 1

Reel/Frame: 013887/0766 **Recorded:** 08/21/2003 **Pages:** 3

Conveyance: CHANGE OF NAME (SEE DOCUMENT FOR DETAILS).

Assignor: RHONE-POULENC RORER PHARMACEUTICALS INC. **Exec Dt:** 12/15/1999

Assignee: AVENTIS PHARMACEUTICALS INC.
300 SOMERSET CORPORATE BOULEVARD
BRIDGEWATER, NEW JERSEY 08807

Correspondent: AVENTIS PHARMACEUTICALS INC.
KAREN I. KRUPEN
ROUTE 202-206/P.O. BOX 6800
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Search Results as of: 12/16/2003 1:46:45 P.M.

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PATENT AND TRADEMARK OFFICE

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Date August 21, 2003
Signature [signature]

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1. Name of conveying party(ies):
Rhone-Poulenc Rorer Pharmaceuticals Inc.

Additional name(s) of conveying party(ies) attached? ☐ YES ☒ NO

2. Name and address of receiving party(ies):

Name: **Aventis Pharmaceuticals Inc.**
Internal Address:
Street Address: **300 Somerset Corporate Boulevard**
City: **Bridgewater** State: **NJ** ZIP: **08807**

Additional name(s) and address(es) attached? ☐ YES ☒ NO

3. Nature of Conveyance:
☐ Assignment ☐ Merger
☐ Security Agreement ☒ Change of Name
☐ Other

Execution Date: **12/15/1999**

4. Application number(s) or patent number(s):
If this document is being filed together with a new application, the execution date of the application is:

A. Patent Application No.(s):

B. Patent No.(s): **6,217,866**

Additional numbers attached? ☐ YES ☒ NO

5. Name and address of party to whom correspondence concerning document should be mailed:

Name: **Karen I. Krupen, Reg. No. 34,647**
Internal Address: **Aventis Pharmaceuticals Inc.**
Street Address: **Route 202-206 / P.O. Box 6800**
City: **Bridgewater** State: **NJ** ZIP: **08807-0800**
**** FAX NUMBER: (908) 231-2626 ****
Our Reference No.: **USA0207-US-CNT-1**

6. Total number of applications and patents involved:

7. Total (37 CFR 3.41): **$40.00**

☐ Enclosed
☒ Authorized to be charged to deposit account

8. Deposit account number: **18-1982**

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To the best of my knowledge and belief, the foregoing information is true and correct and any attached copy is a true copy of the original document.

Karen I. Krupen, Reg. No. 34,647
Name of Person Signing

[signature]
Signature

Date: **August 14, 2003**
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700041094

State of Delaware

Office of the Secretary of State

I, EDWARD J. FREEL, SECRETARY OF STATE OF THE STATE OF DELAWARE, DO HEREBY CERTIFY THE ATTACHED IS A TRUE AND CORRECT COPY OF THE CERTIFICATE OF AMENDMENT OF "RHONE-POULENC RORER PHARMACEUTICALS INC.", CHANGING ITS NAME FROM "RHONE-POULENC RORER PHARMACEUTICALS INC." TO "AVENTIS PHARMACEUTICALS PRODUCTS INC.", FILED IN THIS OFFICE ON THE FIFTEENTH DAY OF DECEMBER, A.D. 1999, AT 11:30 O'CLOCK A.M.

Edward J. Freel, Secretary of State

0631221 8100

991542800

AUTHENTICATION: 0145888

DATE: 12-16-99

CERTIFICATE OF AMENDMENT
OF
CERTIFICATE OF INCORPORATION
OF
RHONE-POULENC RORER PHARMACEUTICALS INC.

The undersigned, being officers of Rhône-Poulenc Rorer Pharmaceuticals Inc. (the "Company"), for the purpose of amending the Certificate of Incorporation pursuant to the provisions of Sections 228 and 242 of the Delaware General Corporation Law, hereby execute the following Certificate of Amendment:

FIRST: The name of the corporation is RHÔNE-POULENC RORER PHARMACEUTICALS INC.

SECOND: The following amendment was adopted by the directors and sole shareholder in the manner prescribed by the Delaware General Corporation Law.

Article FIRST of the Certificate of Incorporation is hereby amended to read as follows:

"The name of the corporation is Aventis Pharmaceuticals Products Inc."

IN WITNESS WHEREOF, the undersigned have caused this Certificate of Amendment of the Certificate of Incorporation to be duly executed by its Senior Vice President and attested by its Assistant Secretary this 15th day of December, 1999.

RHÔNE-POULENC RORER PHARMACEUTICALS INC.

By: _____
John R. Leone
Senior Vice President & General Manger

C

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

APPOINTMENT OF AGENT CONCERNING APPLICATION FOR PATENT TERM EXTENSION

I, Ross J. Oehler, Vice President, Head, US Patent Operations, have authority for Aventis Pharmaceuticals Inc., the undersigned applicant for patent term extension, to appoint an agent to apply for a patent term extension concerning the below identified patent. Pursuant to this authority, I hereby appoint Tom C. Gallagher of ImClone Systems Incorporated, with an office at

180 Varick Street
New York, NY 10014

as the agent for the Aventis Pharmaceuticals Inc. to further the application for patent term extension concerning the below identified patent.

TITLE OF INVENTION	Monoclonal Antibodies Specific to Human Epidermal Growth Factor Receptor and Therapeutic Methods Employing Same
PATENT NUMBER	6,217,866
FILING DATE	June 7, 1995
ISSUE DATE	April 17, 2001
INVENTORS	Schlessinger, et al.
APPLICANT'S AGENT	ImClone Systems Incorporated
ADDRESS	180 Varick Street New York, NY 10014

DATE: 4/7/04 SIGNATURE: _____

Name: Ross J. Oehler, Reg. No. 33,270
Title: Vice President, Head, US Patent Operations
Aventis Pharmaceuticals Inc.

US006217866B1

(12) **United States Patent**
Schlessinger et al.

(10) **Patent No.: US 6,217,866 B1**
(45) **Date of Patent: Apr. 17, 2001**

(54) **MONOCLONAL ANTIBODIES SPECIFIC TO HUMAN EPIDERMAL GROWTH FACTOR RECEPTOR AND THERAPEUTIC METHODS EMPLOYING SAME**

(75) Inventors: **Joseph Schlessinger**, New York, NY (US); **David Givol**, Rehovot (IL); **Francoise Bellot**, Fresnes (FR); **Richard Kris**, Tucson, AZ (US); **George A. Ricca**, Blue Bell, PA (US); **Christopher Cheadle**, West Chester, PA (US); **Victoria J. South**, Audubon, PA (US)

(73) Assignee: **Rhone-Poulenc Rorer International (Holdings), Inc.**, Greenville, DE (US)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

(21) Appl. No.: **08/487,761**

(22) Filed: **Jun. 7, 1995**

Related U.S. Application Data

(63) Continuation of application No. 08/086,411, filed on Jun. 29, 1993, now abandoned, which is a continuation-in-part of application No. 07/760,852, filed on Sep. 17, 1991, now abandoned, which is a continuation-in-part of application No. 07/244,737, filed on Sep. 15, 1988, now abandoned, which is a continuation of application No. 07/319,109, filed on Mar. 3, 1989, now abandoned.

(51) **Int. Cl.**[7] **A61K 39/395**; C07K 16/28

(52) **U.S. Cl.** **424/143.1**; 424/130.1; 424/138.1; 424/141.1; 424/152.1; 424/155.1; 424/156.1; 530/388.1; 530/388.2; 530/388.22; 530/388.8; 530/388.85

(58) **Field of Search** 424/130.1, 138.1, 424/141.1, 143.1, 152.1, 155.1, 156.1; 530/388.1, 388.2, 388.22, 388.8, 388.85

(56) **References Cited**

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* cited by examiner

Primary Examiner—Nancy A. Johnson
(74) *Attorney, Agent, or Firm*—Hoffmann & Baron, LLP; Irving N. Feit

(57) **ABSTRACT**

Hybridoma cell lines producing monoclonal antibodies specific to the human epidermal growth factor receptor are disclosed. The antibodies are capable of inhibiting the growth of human tumor cells expressing human epidermal growth factor receptors. Therapeutic uses of these monoclonal antibodies by themselves and in combination with anti-neoplastic agents are also disclosed.

9 Claims, 17 Drawing Sheets

FIG. 1

THE EFFECT OF mAb 108.4, DOXORUBICIN AND THEIR COMBINATION

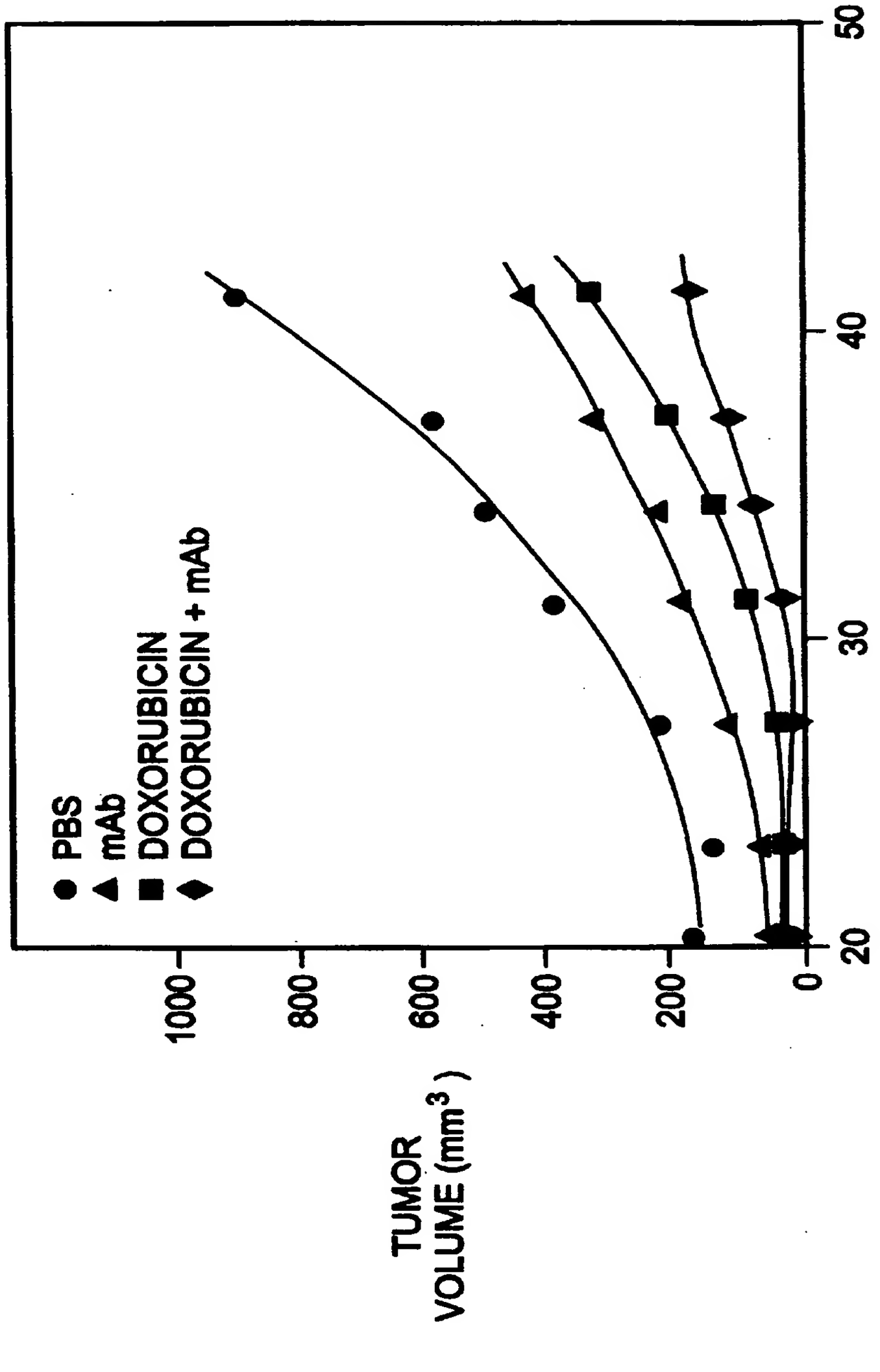
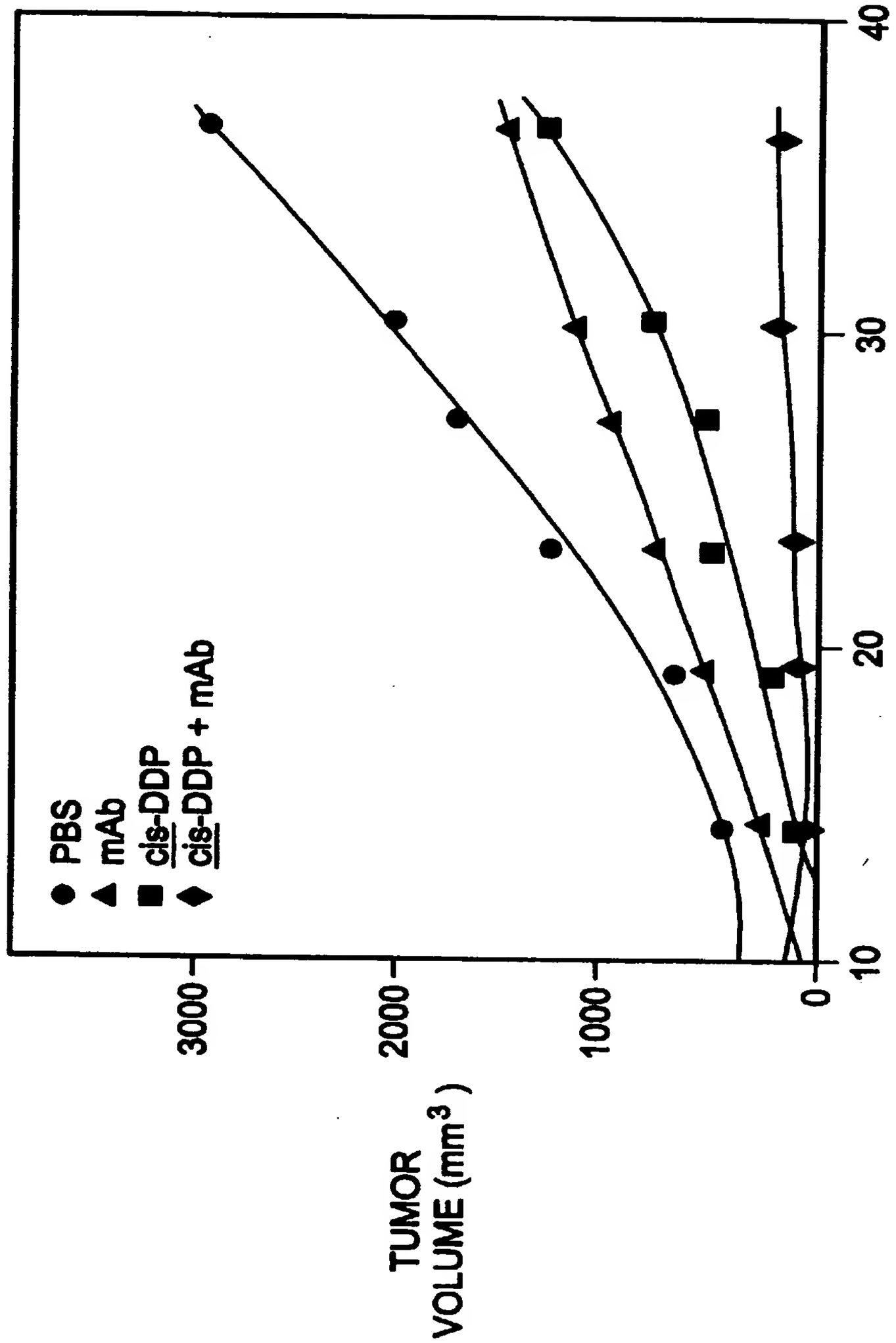


FIG. 2 THE EFFECT OF 108.4 mAb, cis-DDP AND THEIR COMBINATION



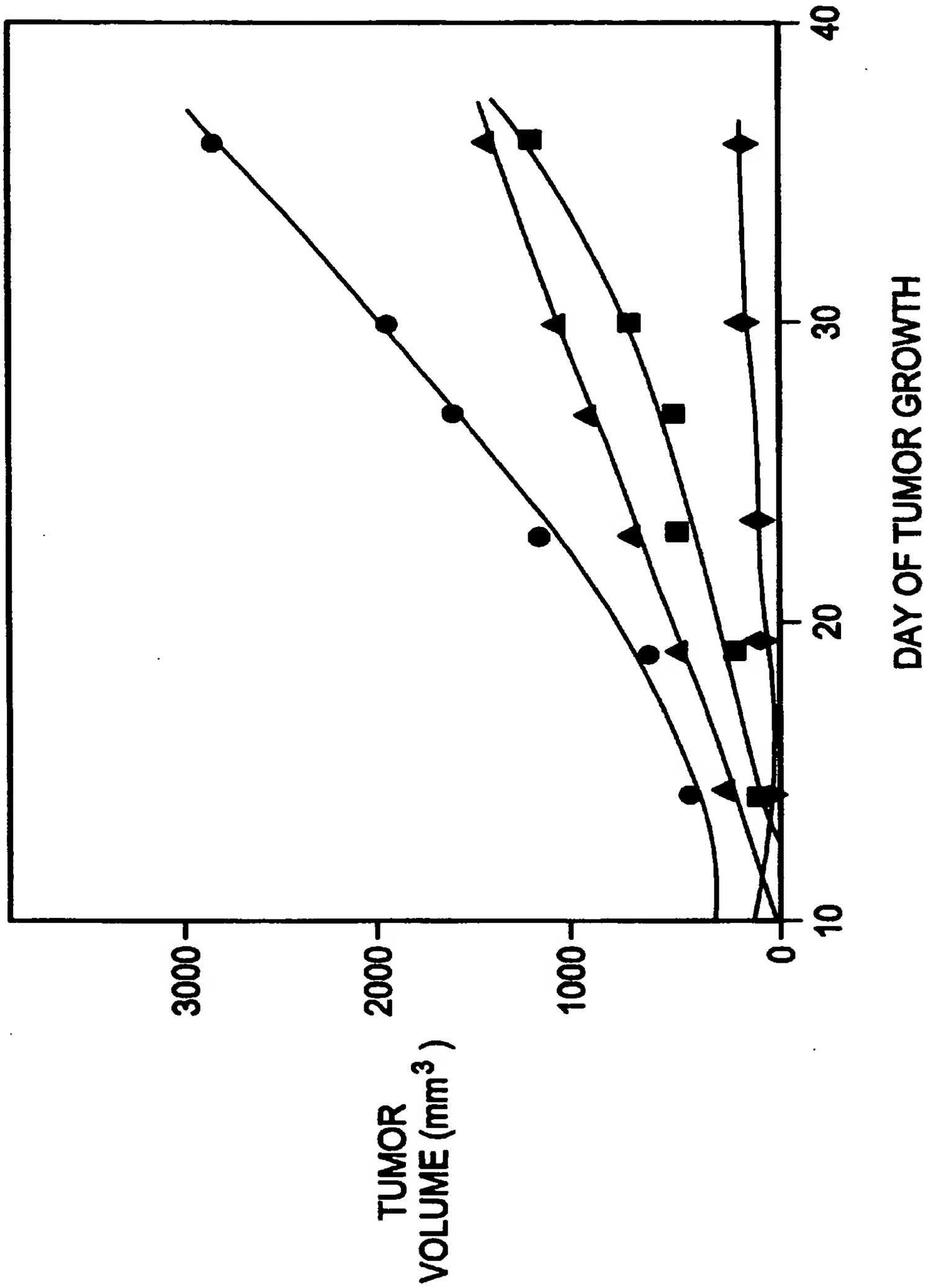

TUMOR VOLUME (mm^3)
3000
2000
1000
0
10
20
30
40
DAY OF TUMOR GROWTH

FIG. 3

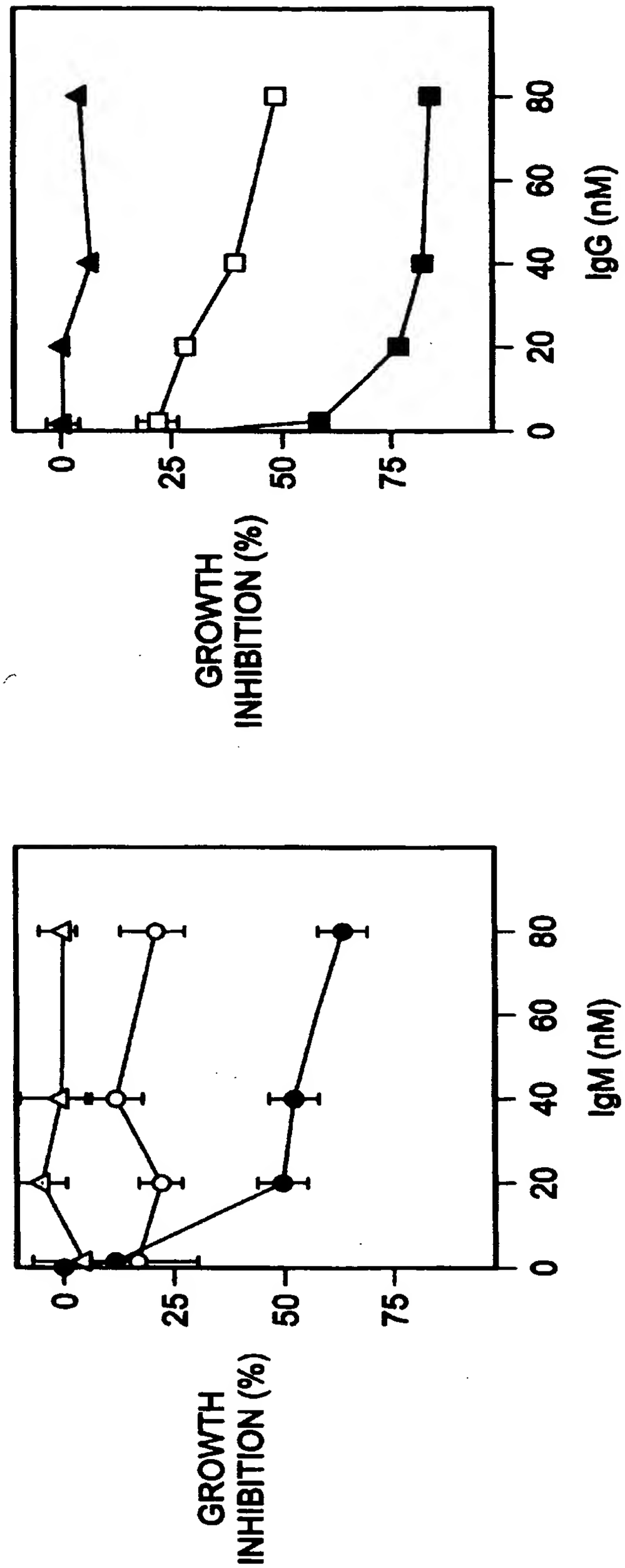

IgG (nM)
0
20
40
60
80
GROWTH INHIBITION (%)
0
25
50
75

FIG. 4B

IgM (nM)
0
20
40
60
80
GROWTH INHIBITION (%)
0
25
50
75

FIG. 4A

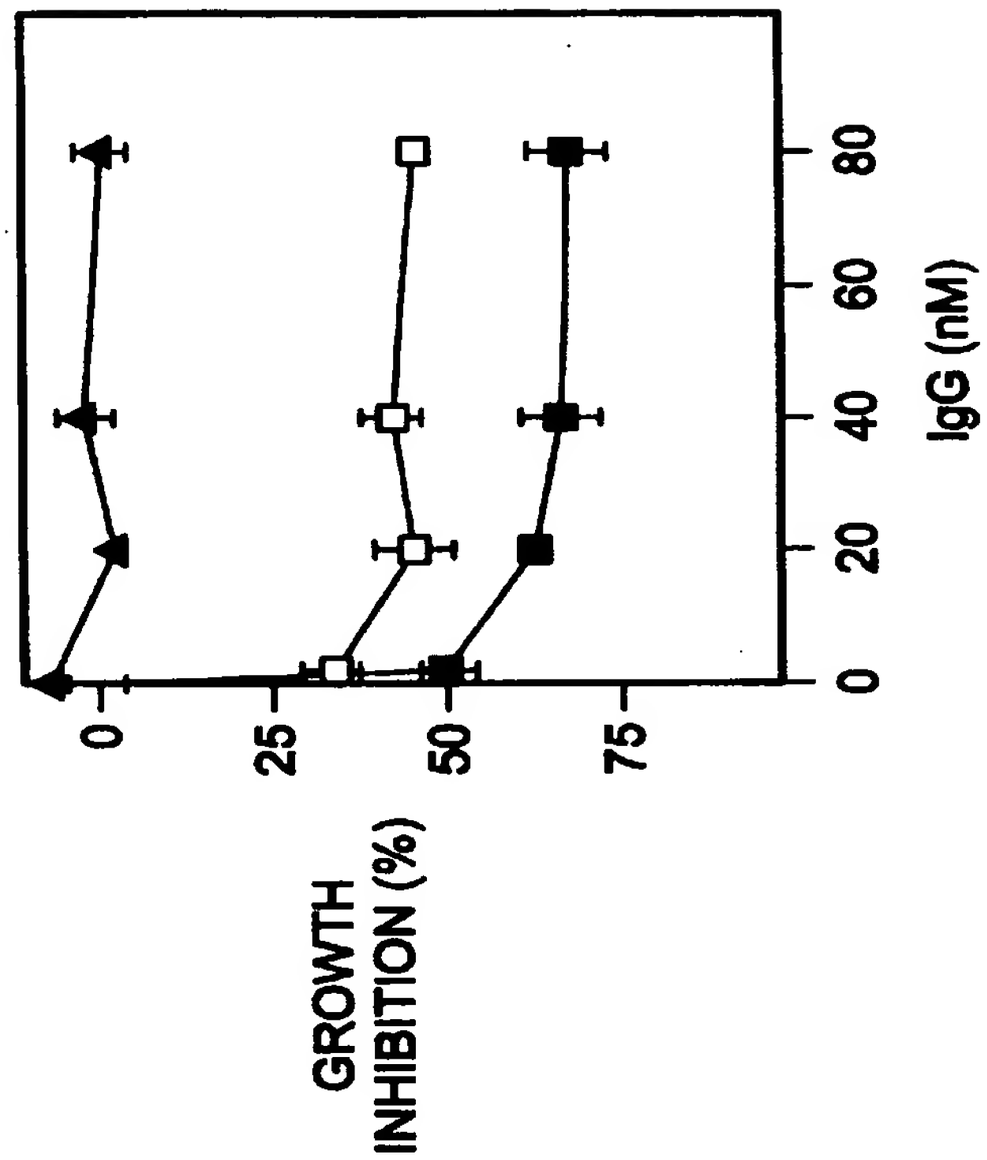

IgG (nM)
0
20
40
60
80
GROWTH INHIBITION (%)
0
25
50
75

FIG. 4D

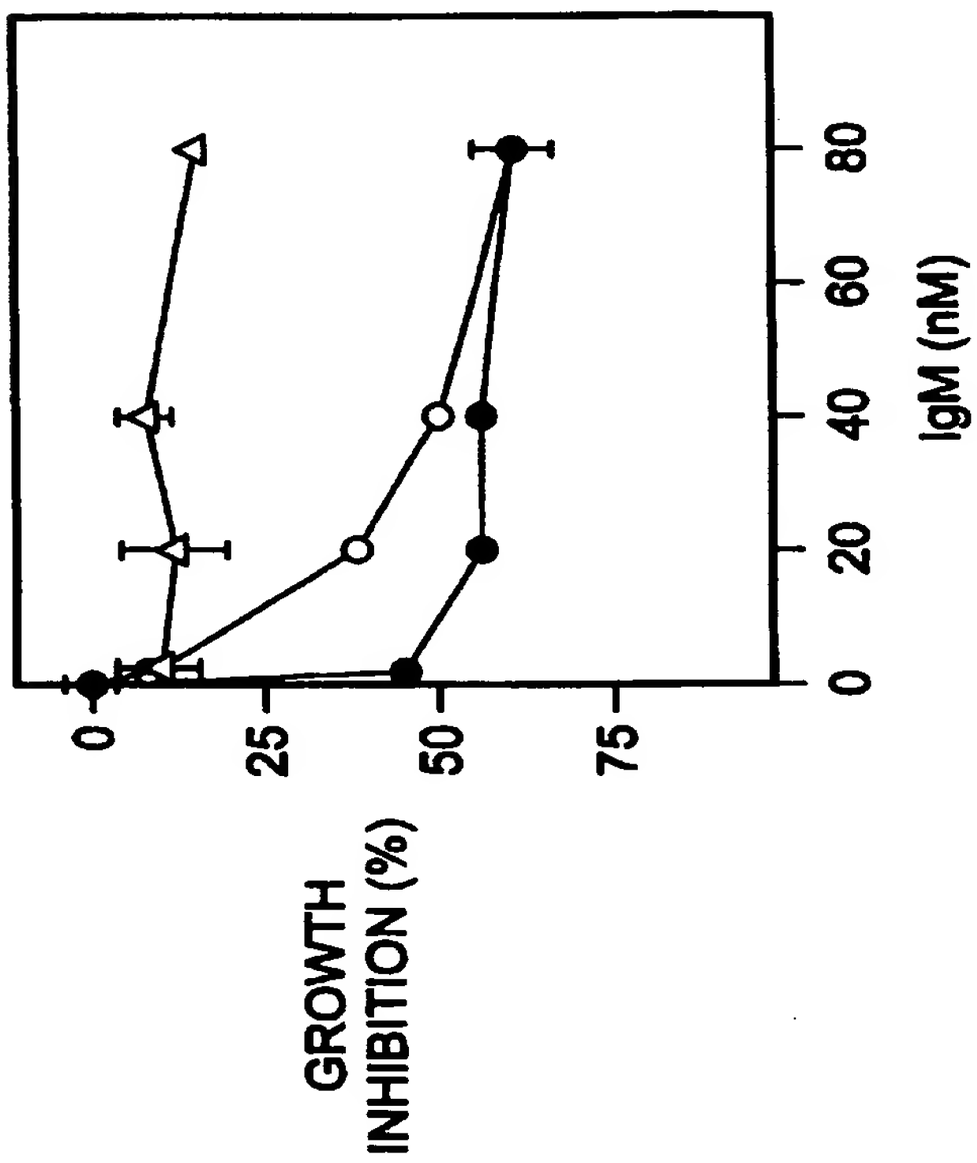

IgM (nM)
0
20
40
60
80
GROWTH INHIBITION (%)
0
25
50
75

FIG. 4C

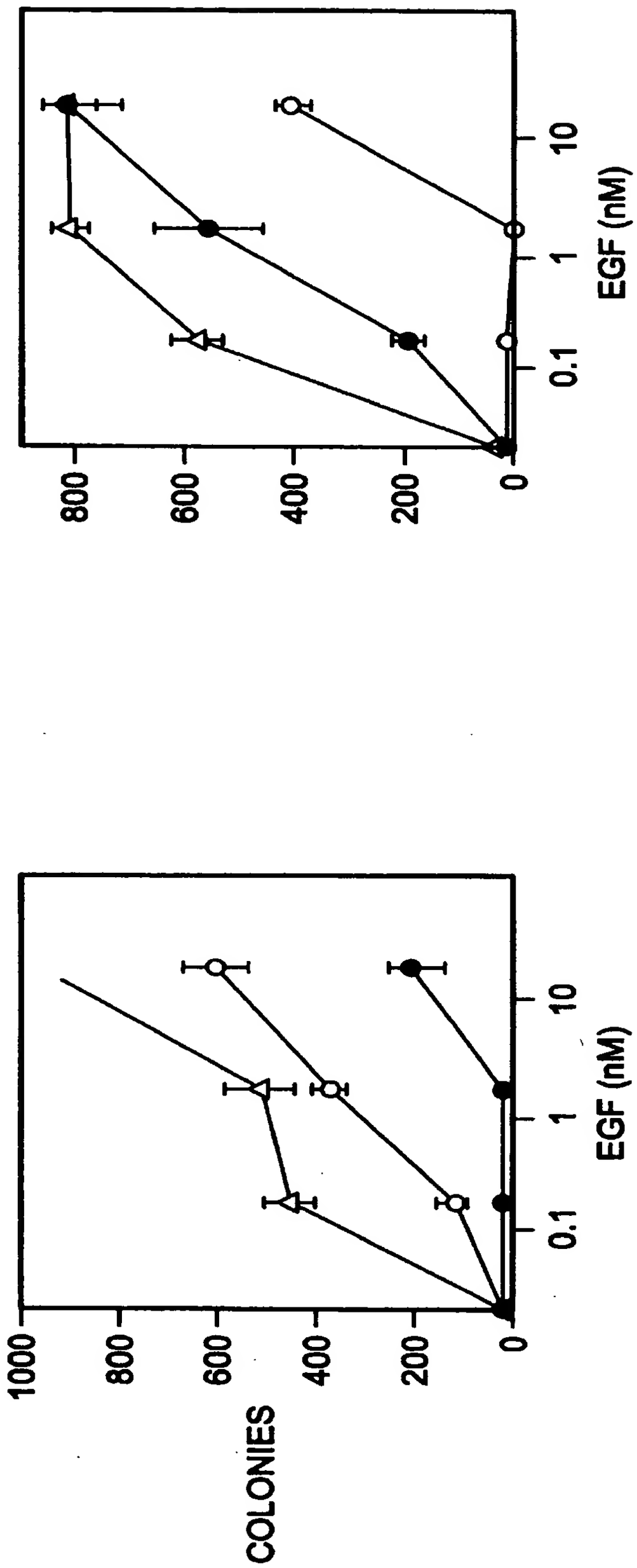

EGF (nM)
10
1
0.1
800
600
400
200
0

FIG. 5B

EGF (nM)
10
1
0.1
1000
800
600
400
200
0
COLONIES

FIG. 5A

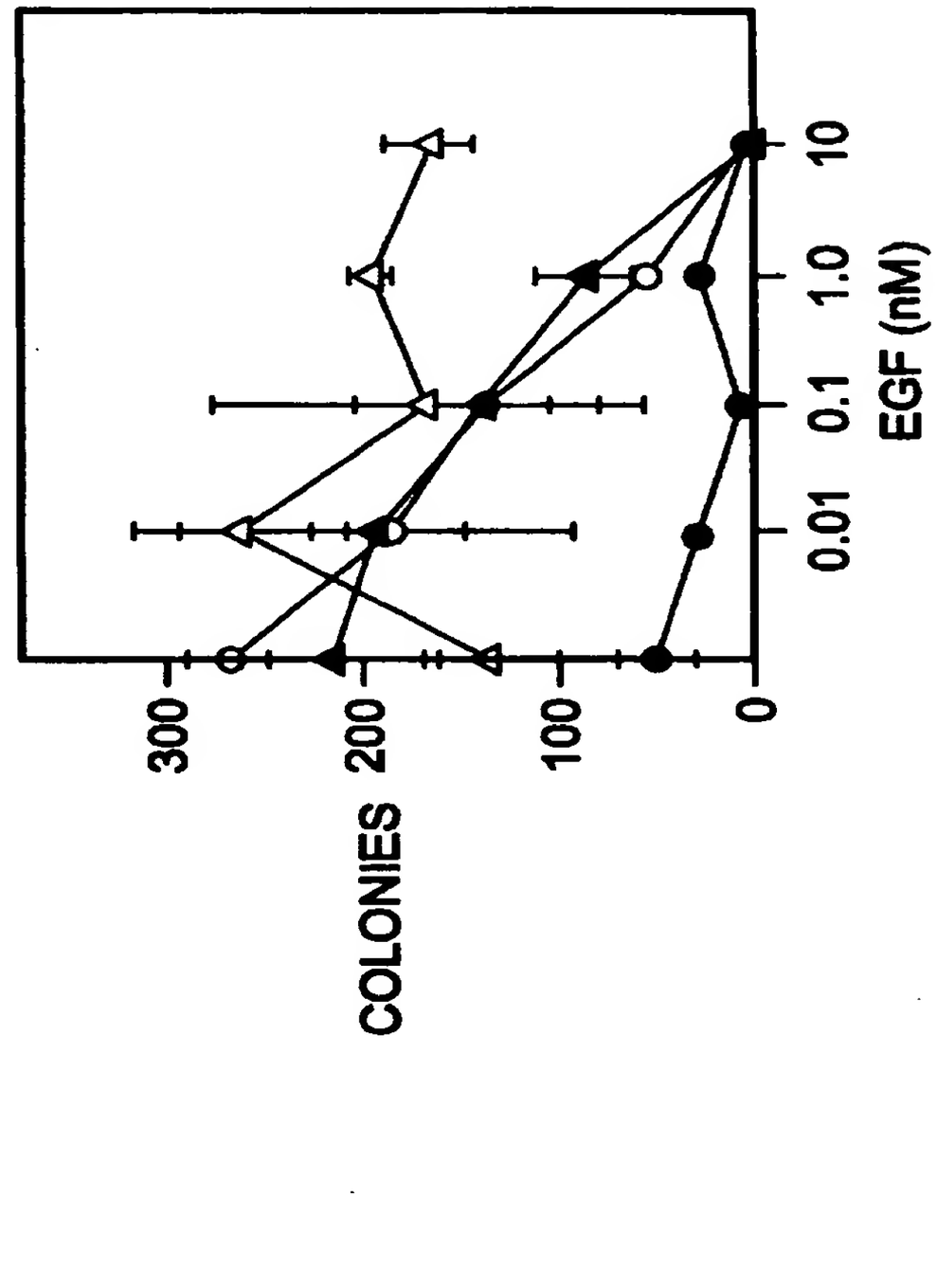

COLONIES
1000
800
600
400
200
0
0.01
0.1
1.0
10
EGF (nM)

FIG. 6A

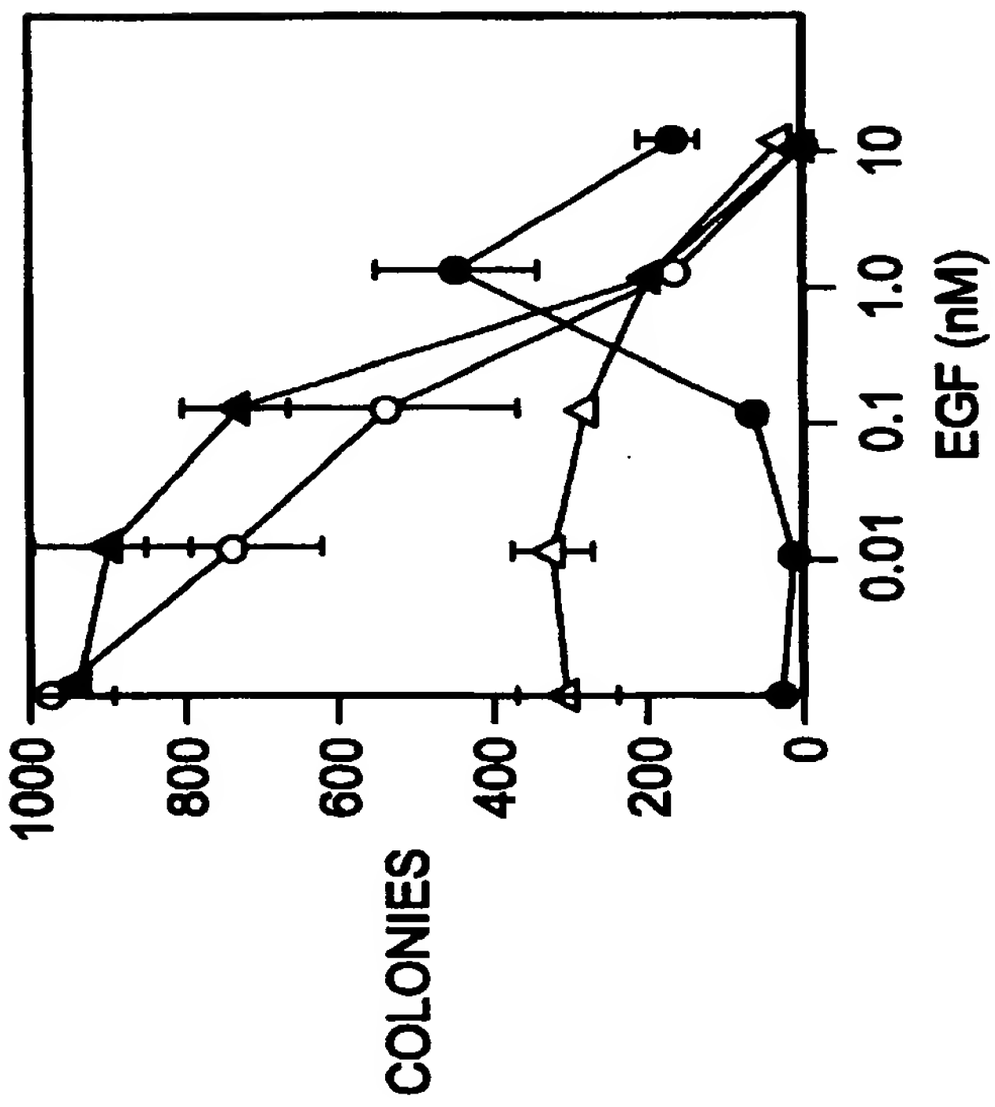

COLONIES
300
200
100
0
0.01
0.1
1.0
10
EGF (nM)

FIG. 6B

FIG. 7

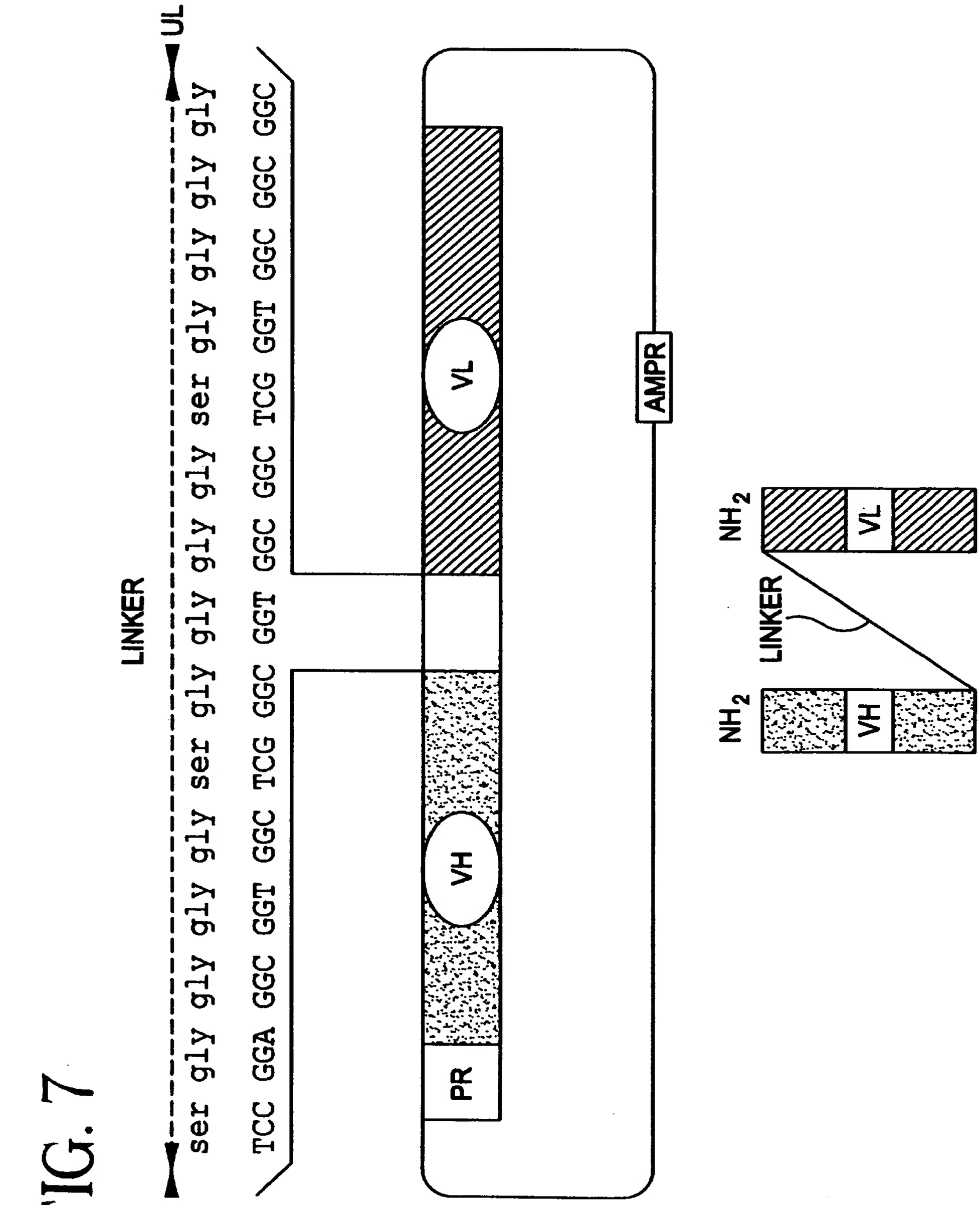

UL
ser gly gly gly gly gly gly ser gly gly gly gly ser
TCC GGA GGC GGT GGC GGC GGC TCG GGC GGT GGC GGC TCG
LINKER
UH
ser gly gly gly gly ser gly gly gly gly ser
TCC GGA GGC GGT GGC GGC GGC TCG GGC GGT GGC GGC TCG
VL
VH
PR
AMPR
NH_2
VL
LINKER
NH_2
VH

FIG. 8

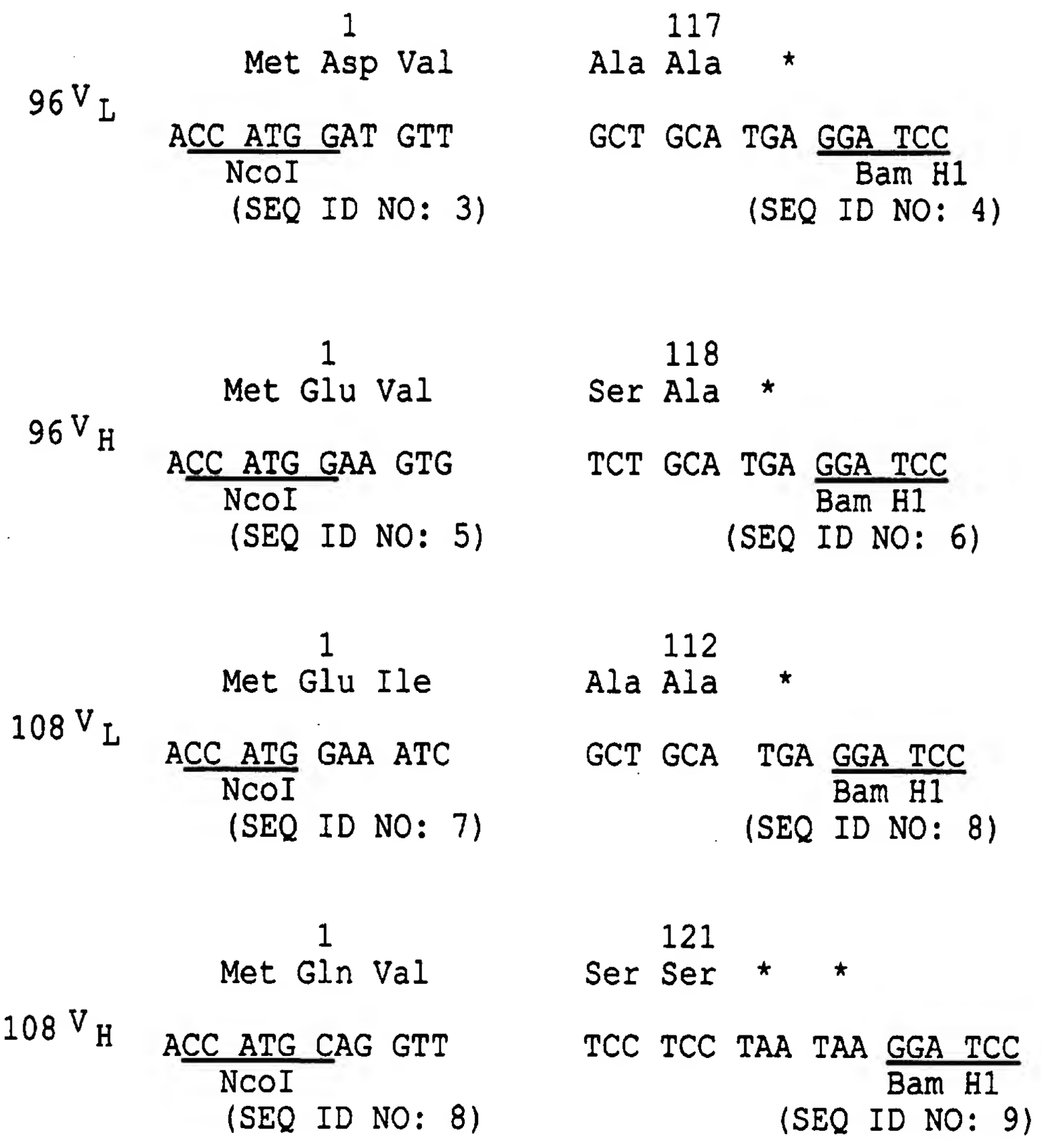

1
Met Asp Val
117
Ala Ala *
96 V L
ACC ATG GAT GTT
NcoI
(SEQ ID NO: 3)
GCT GCA TGA GGA TCC
Bam H1
(SEQ ID NO: 4)
1
Met Glu Val
118
Ser Ala *
96 V H
ACC ATG GAA GTG
NcoI
(SEQ ID NO: 5)
TCT GCA TGA GGA TCC
Bam H1
(SEQ ID NO: 6)
1
Met Glu Ile
112
Ala Ala *
108 V L
ACC ATG GAA ATC
NcoI
(SEQ ID NO: 7)
GCT GCA TGA GGA TCC
Bam H1
(SEQ ID NO: 8)
1
Met Gln Val
121
Ser Ser * *
108 V H
ACC ATG CAG GTT
NcoI
(SEQ ID NO: 8)
TCC TCC TAA TAA GGA TCC
Bam H1
(SEQ ID NO: 9)

FIG. 9

108 VH

```
 1  CAG GTT CAG CTG CAG CAG TCT GGA GCT GAG CTG ATG AAG CCT GGG
 1▶Gln Val Gln Leu Gln Gln Ser Gly Ala Glu Leu Met Lys Pro Gly

46  GCC TCA GTG AAG ATA TCC TGC AAG GCT ACT GGC TAC ACA TTC AGT
16▶Ala Ser Val Lys Ile Ser Cys Lys Ala Thr Gly Tyr Thr Phe Ser

              CDR 1
91  AGT TAC TGG ATA GAG TGG GTA AAG CAG AGG CCT GGA CAT GGC CTT
31▶Ser Tyr Trp Ile Glu Trp Val Lys Gln Arg Pro Gly His Gly Leu

                                                  CDR 2
136  GAG TGG ATT GGA GAG ATT TTA CCG GGA AGT AAA AAA ACT AAC TAC
 46▶Glu Trp Ile Gly Glu Ile Leu Pro Gly Ser Lys Lys Thr Asn Tyr

181  AAT GAG AAG TTC AAG GGA AAG GCC ACA TTC ACT GCA GAT ACA TCC
 61▶Asn Glu Lys Phe Lys Gly Lys Ala Thr Phe Thr Ala Asp Thr Ser

226  TCC AAC ACA GCC TAC ATG CAA TTT AGC AGC CTG ACA TCT GAG GAC
 76▶Ser Asn Thr Ala Tyr Met Gln Phe Ser Ser Leu Thr Ser Glu Asp

                                                        CDR 3
271  TCT GCC GTC TAT TAC TGT GCA AGA TAT TAC TAT AGG AAC GAC GAC
 91▶Ser Ala Val Tyr Tyr Cys Ala Arg Tyr Tyr Tyr Arg Asn Asp Asp

316  TAT GGT ATG GAC TAC TGG GGT CAA GGA ACC TCA GTC ACC GTC TCC
106▶Tyr Gly Met Asp Tyr Trp Gly Gln Gly Thr Ser Val Thr Val Ser

361  TCA
121▶Ser
```

FIG. 10

108 VL

```
 1  GAA ATC CAC ATG ACA CAG ACT ACA TCC TCC CTG TCT GCC TCT CTG
 1▶Glu Ile His Met Thr Gln Thr Thr Ser Ser Leu Ser Ala Ser Leu

                                                      CDR 1
46  GGA GAC AGA GTC ACC ATC AGT TGC AGT GCA AGT CAG GAC ATC AGG
16▶Gly Asp Arg Val Thr Ile Ser Cys Ser Ala Ser Gln Asp Ile Arg

91  AAT TAT TTA AAC TGG TAT CAG CAG AAA CCT GAT GGA ACT GTT AAA
31▶Asn Tyr Leu Asn Trp Tyr Gln Gln Lys Pro Asp Gil Thr Val Lys

                    CDR 2
136 CTC CTG ATC TAT TAC ACA TCA ACT TTA CAT TCA GGA GTC CCA TCA
 46▶Leu Leu Ile Tyr Tyr Thr Ser Thr Leu His Ser Gly Val Pro Ser

181 AGG TTC AGT GGC AGC GGG TCT GGG ACA GAT TAT TCT CTC ACC ATC
 61▶Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Tyr Ser Leu Thr Ile

226 AGC AAC CTG GAA CCT GAA GAT ATT GCC ACT TAT TAT TGT CAG CAG
 76▶Ser Asn Leu Glu Pro Glu Asp Ile Ala Thr Tyr Tyr Cys Gln Gln

                CDR 3
271 TAT AGT AAG ATT CCG TAC ACG TTC ACA GGG GGG ACC AAG CTG GAA
 91▶Tyr Ser Lys Ile Pro Tyr Thr Phe Thr Gly Gly Thr Lys Leu Glu

316 ATA AAA|CGG GCT GAT GCT GCA
106▶Ile Lys|Arg Ala Asp Ala Ala
```

FIG. 11

96 VH

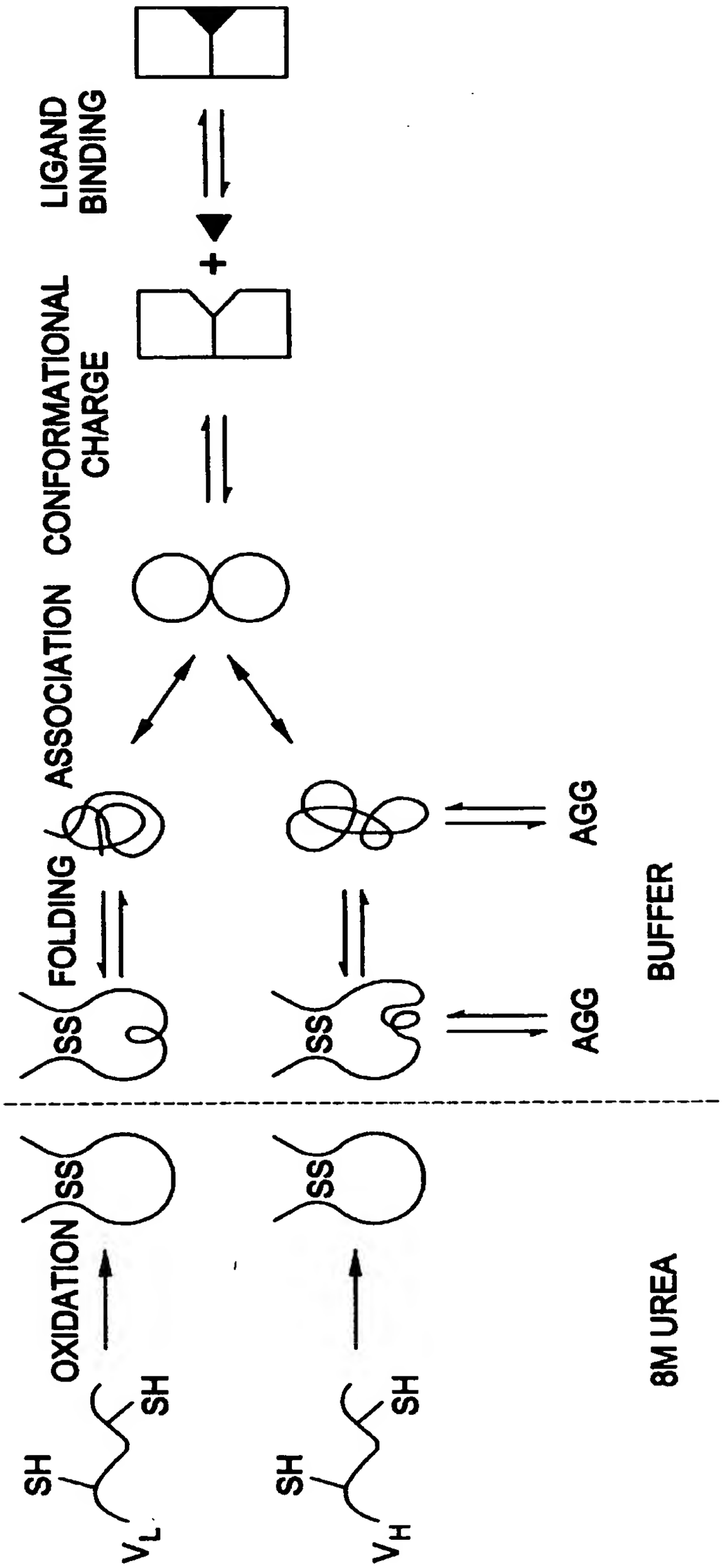
```
 1  GAA GTG CAG CTG GTG GAG TCT GGG GGA GGC TTA GTG AGG CCT GGA GGG
 1 ▶Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Ara Pro Gly Gly

49  TCC CTG AAA CTC TCC TGT GCA GCC TCT GGA TTC GCT TTC AGT AAC TAT
17 ▶Ser Leu Lys Leu Ser Cys Ala Ala Ser Gly Phe Ala Phe Ser Asn Tyr

          CDR 1
97  GAC ATG TCT TGG GTT CGC CAG ACT CCG GAG AAG AGG CTG GAG TGG GTC
33 ▶Asp Met Ser Trp Val Arg Gln Thr Pro Glu Lys Arg Leu Glu Trp Val

                                CDR 2
145  GCG TAC ATT GGT AAT GGT GGT AAC ACC TAC TCT CCA GAC ACT GTG AAG
 49 ▶Ala Tyr Ile Gly Asn Gly Gly Asn Thr Tyr Ser Pro Asp Thr Val Lys

193  GGC CGA TTC ACC ATC TCC AGA GAC AAT GCC GAG AAC ACC CTA TAC CTT
 65 ▶Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Glu Asn Thr Leu Tyr Leu

241  CAA ATG AGC AGT CTG AAG TCT GAG GAC ACA GCC ATT TAT TAC TGT GCA
 81 ▶Gln Met Ser Ser Leu Lys Ser Glu Asp Thr Ala Ile Tyr Tyr Cys Ala

                          CDR 3
289  AGT CAC TAT GGT TAC GAC GGG AGG TTT GCT TAC TGG GGC CAA GGG ACT
 97 ▶Ser His Tyr Gly Tyr Asp Gly Arg Phe Ala Tyr Trp Gly Gln Gly Thr

337  CTG GTC ACT GTC TCT GCA
113 ▶Leu Val Thr Val Ser Ala
```

FIG. 12

96 VL

```
   1  GAT GTT GTG ATG ACC CAA AGT CCA CTC TCC CTG CCT GTC AGT
   1▶Asp Val Val Met Thr Gln Ser Pro Leu Ser Leu Pro Val Ser

  43  CTT GGA GAT CAA GCC ACC ATC TCT TGC AGA TCT AGT CAG AGC
  15▶Leu Gly Asp Gln Ala Thr Ile Ser Cys Arg Ser Ser Gln Ser

      CDR 1
  85  CTT GAA CAC AGT AAT GGA GAC ACC TAT TTA CAT TGG TAC CTG
  29▶Leu Glu His Ser Asn Gly Asp Thr Tyr Leu His Trp Tyr Leu

 127  CAG AAG GCA GGC CAG TCT CCA AAG CTC CTG ATC TAC AAA GTT
  43▶Gln Lys Ala Gly Gln Ser Pro Lys Leu Leu Ile Tyr Lys Val

      CDR 2
 169  TCC AAC CGA TTT TCT GGG GTC CCG GAT AGG TTC AGT GGC AGT
  57▶Ser Asn Arg Phe Ser Gly Val Pro Asp Arg Phe Ser Gly Ser

 211  GGA TCA GGG ACA GAT TTC ACA CTC AAG ATC AGC AGA GTG GAG
  71▶Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile Ser Arg Val Glu

                                                        CDR 3
 253  GCT GAG GAT CTG GGA GTT TAT TTC TGC TGT CAA AGT ACA CAT
  85▶Ala Glu Asp Leu Gly Val Tyr Phe Cys Cys Gln Ser Thr His

 295  GTT CCG TGG ACG TTC GGT GGA GGC ACC AAC CTG GAA ATC AAA
  99▶Val Pro Trp Thr Phe Gly Gly Gly Thr Asn Leu Glu Ile Lys

 337  CGG GCT GAT GCT GCA
   1  Arg Ala Asp Ala Ala
```

FIG. 13


LIGAND BINDING
+
CONFORMATIONAL CHARGE
ASSOCIATION
FOLDING
SS
AGG
AGG
SS
BUFFER
OXIDATION
SS
SH
SH
V_L
SS
SH
SH
V_H
8M UREA

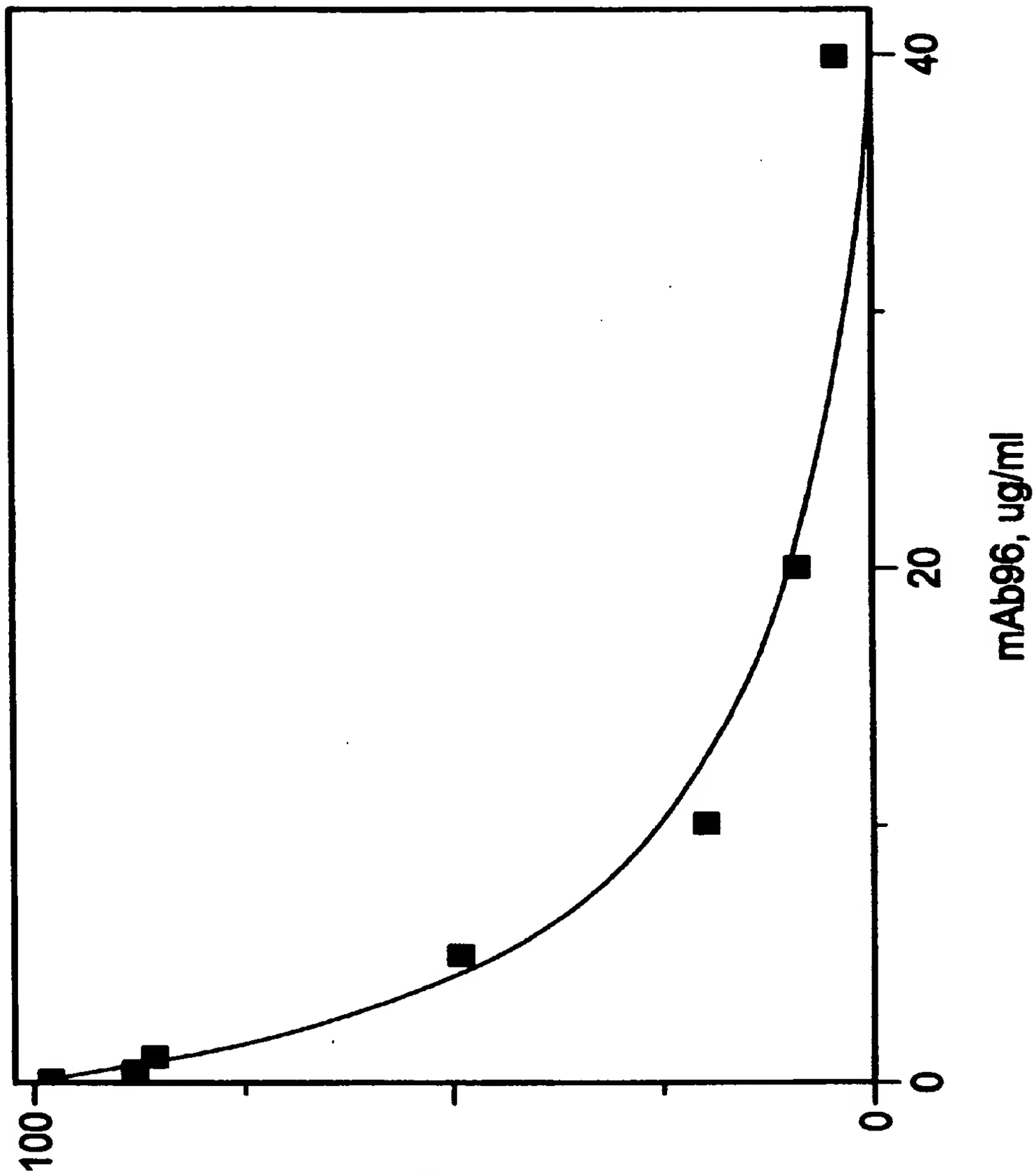


FIG. 14 mAb96 COMPETION / IODINATED mAb96 VS mAb96

FIG. 15 96 rFv COMPETION / IODINATED mAbB96 VS 96 rFv

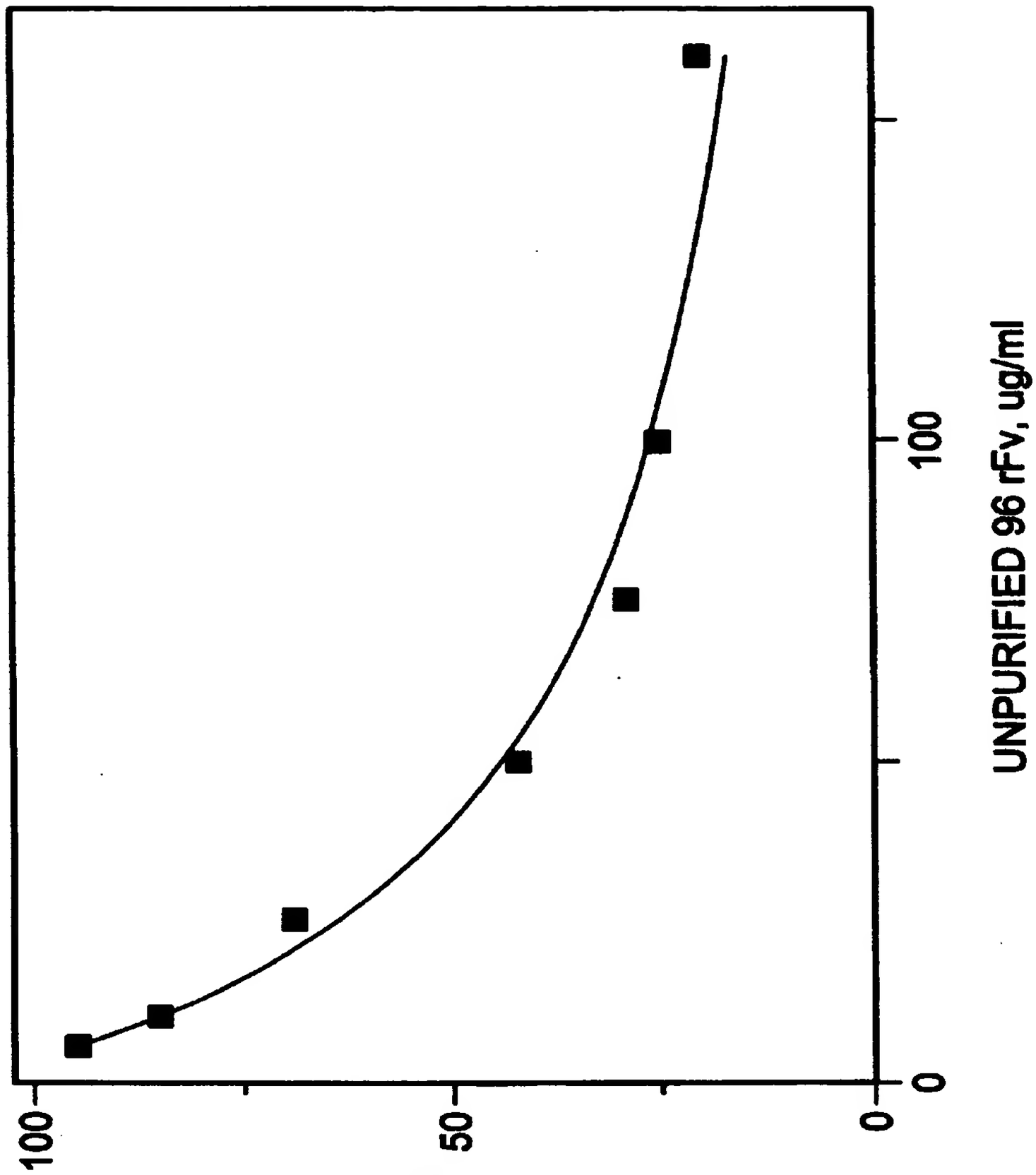
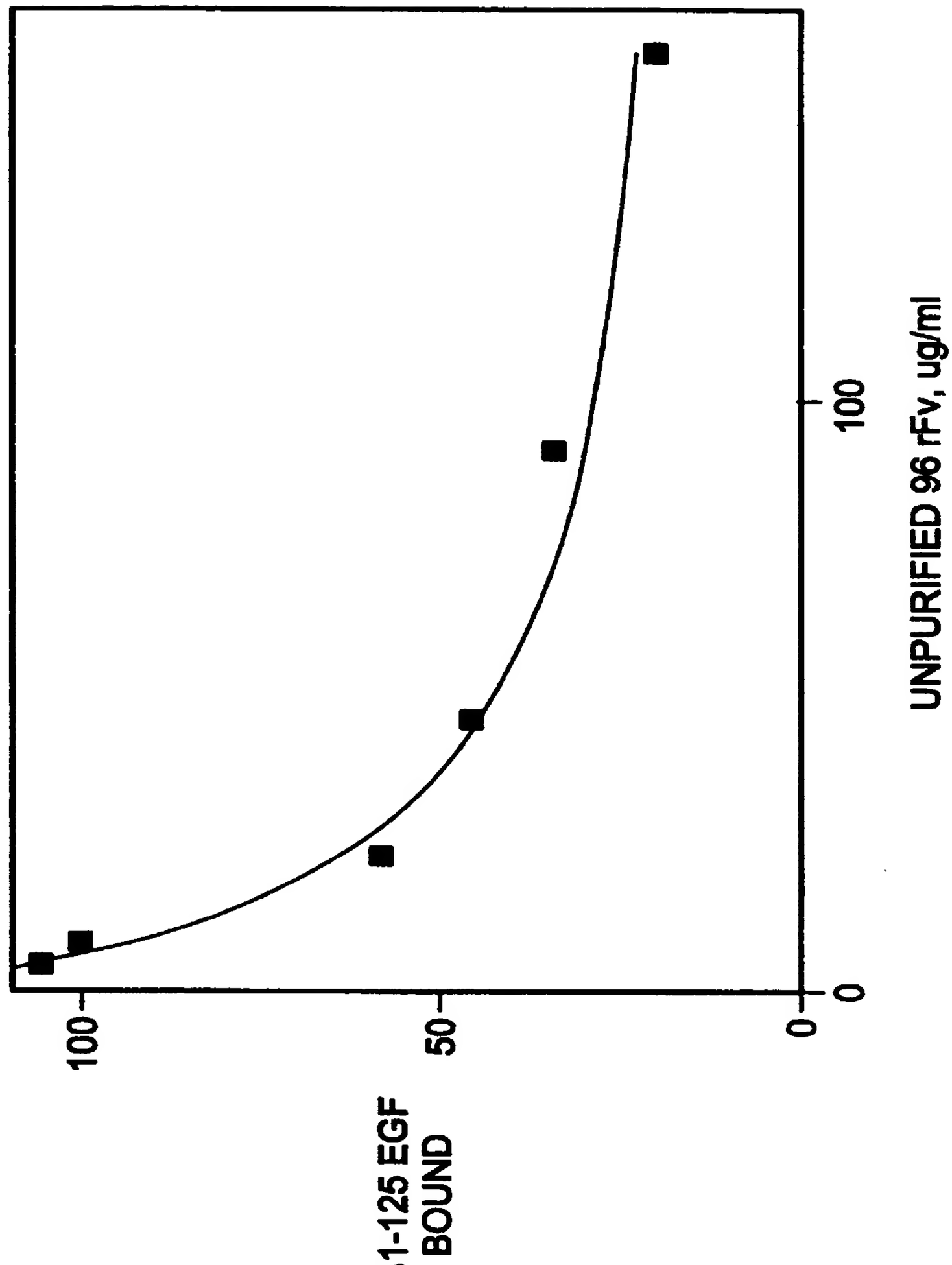


FIG. 16 96 rFv COMPETION / IODINATED EGF VS 96 rFv



MONOCLONAL ANTIBODIES SPECIFIC TO HUMAN EPIDERMAL GROWTH FACTOR RECEPTOR AND THERAPEUTIC METHODS EMPLOYING SAME

RELATED APPLICATIONS

This is a continuation of application Ser. No. 08/086,411 filed on Jun. 29, 1993, now abandoned, which is a continuation-in-part of U.S. application Ser. No. 07/760,852, filed Sep. 17, 1991 now abandoned, which is a continuation-in-part of Ser. No. 07/244,737, filed Sep. 15, 1988, now abandoned, and a continuation of Ser. No. 07/319,109, filed Mar. 3, 1989, now abandoned.

BACKGROUND OF THE INVENTION

This invention relates to new hybrid cell lines and in particular to hybrid cell lines for production of monoclonal antibodies specific to a human receptor for epidermal growth factor (EGF) which can inhibit the growth of human tumor cells that express human EGF receptors, to the antibodies so produced, to therapeutic methods employing the antibodies, and to therapeutic methods employing the antibodies in combination with anti-neoplastic agents.

Control of cell growth is regulated by the interaction of soluble growth factors and cell membrane receptors.

The first step in the mitogenic stimulation of epidermal cells is the specific binding of epidermal growth factor (EGF) to a membrane glycoprotein known as the epidermal growth factor receptor (EGF receptor). (Carpenter, et al., Epidermal Growth Factor, *Annual Review Biochem.,* Vol. 48, 193–216 (1979)). The EGF receptor is composed of 1,186 amino acids which are divided into an extracellular portion of 621 residues and a cytoplasmic portion of 542 residues connected by a single hydrophobic transmembrane segment of 23 residues. (Ullrich et al., Human Epidermal Growth Factor cDNA Sequence and Aberrant Expression of the Amplified Gene in A-431 Epidermoid Carcinoma Cells, *Nature,* Vol. 309, 418–25 (1986)). The external portion of the EGF receptor can be subdivided into four domains. Recently, it has been demonstrated that domain III, residues 333 to 460, which is flanked by two cysteine domains is likely to contain the EGF binding site of the receptor. (Lax, et al., Localization of a Major Receptor-Binding Domain for Epidermal Growth Factor by Affinity Labeling, *Mol. and Cell Biol.,* Vol. 8, 1831–1834 (1988)). The binding of EGF to domain III leads to the initiation of pleiotropic responses leading to DNA synthesis and cell proliferation.

It has been found in various types of human tumor cells that those cells overexpress EGF receptors. For example, the cancerous cells of bladder tumors have been shown to have a relatively large population of EGF receptors. (Neal et al., Epidermal Growth Factor Receptor in Human Bladder Cancer: Comparison of Invasive and Superficial Tumors, *Lancet,* Vol. 1, 366–367 (1985)). Breast cancer cells exhibit a positive correlation between EGF receptor density and tumor size and a negative correlation with the extent of differentiation. (Sainsbury et al., Epidermal Growth Factor Receptors and Oestrogen Receptors in Human Breast Cancer. *Lancet,* Vol. 1, 364–366 (1985); Presence of Epidermal Growth Factor Receptor as an Indicator of Poor Prognosis In Patients With Breast Cancer. *J. Clin. Path.,* Vol. 38, 1225–1228; Epidermal-Growth-Factor Receptor Status as Predictor of Early Recurrence and Death From Breast Cancer. *Lancet,* Vol.1, 1398–1400 (1987). The tumorigenicity of a series of human vulval epidermoid carcinoma (A431) clonal variants implanted into athymic mice having different

levels of EGF receptors was found to correlate directly with the level of expression of the EGY receptor (Santon et al., Effects of Epidermal Growth Factor Receptor Concentration on Tumorigenicity of A431 cells in nude mice. *Cancer Res.,* Vol. 46, 4701–4700 (1986)). Thus, it has been proposed that overexpression of EGF receptors play a role in the origin or tumorigenesis of cancer cells.

The influence of EGF receptor density on the biological behavior of cancer cells may be mediated by the interaction of the receptor with its ligands—namely, EGF or transforming growth factor (TGF). In the majority of cells, when EGF binds to a specific region of the EGF receptor, the cell is mitogenically stimulated. Other tumor cells, such as A431 cells are not mitogenically stimulated by the binding of EGF to its receptors.

Two groups have reported in vivo growth inhibition of tumor A431 cell xenografts in nude mice by binding monoclonal antibodies to the epidermal growth factor receptor of the tumorous cells. Masui et al. demonstrated that treatment with anti-EGF receptor monoclonal antibodies of the IgG2a and IgGI isotype completely prevented tumor formation in athymic mice by subcutaneously implanted A431 cells when treatment was started on the day of tumor cell inoculation. (Masui et al., Growth Inhibition of Human Tumor Cells in Athymic Mice by Anti Epidermal Growth Factor Receptor Monoclonal Antibodies. *Cancer Res.,* Vol. 44 1002–1007 (1984); Mechanism of Antitumor Activity in Mice for Anti Epidermal Growth Factor Receptor Monoclonal Antibodies With Different Isotypes. *Cancer Res.* Vol. 46 5592–5598 (1986)). Rodeck et al. used a different monoclonal antibody than Masui of the IgG2a isotype which also binds to the EGF receptor of A431 cells to completely inhibit tumor growth of A431 cells xenotransplanted in mice. (Rodeck et al. Tumor Growth Modulation by a Monoclonal Antibody to the Epidermal Growth Factor Receptor: Immunologically Mediated and Effector Cell—Independent Effects. *Cancer Res.,* Vol. 47, 3692–3696 (1987)).

To date, no one, however, has inhibited the in vitro or in vivo growth of human oral epidermoid carcinoma (KB) or human mammary epithelial (184AIN4 and 184AIN4-T—collectively "184") cells. KB and 184 cells are commonly used in studies relating to the EGF-receptor.

KB and 184 cells are substantially different from A431 cells, especially in terms of their growth response to epidermal growth factor. KB and 184 cells are growth stimulated by high concentrations of epidermal growth factor whereas A431 cells are growth inhibited by high concentrations of epidermal growth factor.

Those differences as well as the lack of complete understanding of the mechanism by which the anti-EGF-receptor antibodies inhibit the growth of tumor cells in vivo, prohibit one from accurately determining whether monoclonal antibodies which bind to EGF receptor of A431 cells and demonstrate anti-tumoral activity on A431 cell xenografts in nude mice will also demonstrate antitumoral activity on KB or 184 cell xenografts in nude mice.

Additionally, because human tumor cells are also growth stimulated by epidermal growth factor, KB and 184 cells provide a more representative pattern of responding to EGF than A431 cells, and, in fact, are used as a model for human tumor cells expressing EGF receptors. (Willington et al. *J Cell Biol.,* Vol. 94, 207–212 (1982).

The primary goal in treating tumors is to kill all the cells of the tumor. A therapeutic agent that kills the cell is defined as cytotoxic. A therapeutic agent that merely prevents the cells from replicating, rather than killing the cells, is defined as cytostatic.

Treatment solely with monoclonal antibodies which bind to the EGF receptor merely prevent the cells from replicating, and thus, the monoclonal antibodies act as a cytostatic agent. In order to overcome the monoclonal antibody's cytostatic limitations, monoclonal antibodies specific to the extracellular domain of human epidermal growth factor receptors have been combined with macrophage or mouse complement to yield a cytotoxic response against A431 cells. (Masui et al., Mechanism of Antitumor Activity in Mice for Anti-Epidermal Growth Factor Receptor Monoclonal Antibodies with Different Isotopes, *Cancer Research,* Vol. 46, 5592–5598 (1986)).

Anti-neoplastic or chemotheropeutic agents administered by themselves, are effective cytotoxic agents. The use of anti-neoplastic agents such as doxorubicin (adriamycin) and cisplatin, for example, are well known in the art. Use of those reagents by themselves, however, are only effective at levels which are toxic or subtoxic to the patient. Cisplatin is intravenously administered as a 100 mg/m^2 dose once every four weeks and adriamycin is intravenously administered as a 60–75 mg/m^2 dose one every 21 days.

Bacterial Expression of Antibodies: The prototypical immunoglobulin structure consists of a 150,000 dalton heterodimer composed of two heavy (50,000 daltons each) and two light (25,000 daltons each) chains. Each heavy and light chain pair are covalently attached by a disulfide bond located between the first and second constant domains that joins the carboxy terminal end of the light chain with the heavy chain. The two heavy and light chain pairs are themselves joined together by one or more disulfide bonds, referred to as the hinge region, located between the two heavy chains [1]. Thus, bacterial expression of an entire active immunoglobulin molecule requires, 1) the complex refolding of both heavy and light chains, 2) the concomitant formation of up to 16 disulfide bonds, and 3) the association of protein dimers to form the final divalent molecule.

Initial attempts to produce antibodies in *E. coli* focused on the expression of entire heavy and light chains, either separately or together in the same cell line [2, 3]. Low levels of expression for both chains were reported in 1984 by two separate groups. Cabilly et al. [2] working with an anti-carcinoembryonic antigen antibody (CEA) reported expression levels of 3% and 0.5% (percent of total cellular protein) for heavy and light chains, respectively. Boss et al. [3] working with an anti-4-hydroxy-3-nitrophenyl acetyl (NP) antibody was able to express the light chain (13% of total protein) in a protease deficient cell line (K12 strain E103S) but the same system only yielded 1% heavy chain. Despite these difficulties with expression levels, both groups reported the first successful recovery of antibody activity from genes cloned and expressed in *E. coli.*

Specific antigen binding activity was detected by both groups following reduction, denaturation, and refolding (in the presence of redox reagents) of partially purified chains. No active antibody was detected in a mixture of heavy and light chain whole cell extracts, nor observed in a lysate made from cells coproducing the two chains together [2]. Reported recoveries of activity from the refolding procedures range from 3–5% for the anti-CEA antibody down to as low as 0.007% for the anti-NP antibody. Cabilly found similarly low levels of recovery (0.5%) using native anti-CEA antibody subjected to the same denaturation and renaturation procedures [2]. In addition, Boss observed that the majority of active anti-NP material contained truncated heavy chains, suggesting that the shorter peptides were somehow favored during the refolding process [3]. Finally, the actual formation of complete heterodimeric antibodies remains in doubt since no evidence was obtained for divalency by either group.

Fortunately, it is not necessary to express an entire antibody molecule in order to reproduce its antigen-binding capacity. Native antibody protein can be proteolytically degraded under controlled conditions to yield a number of different fragments, some of which retain the full antibody binding capacity. Digestion with the enzyme papain cleaves the heavy chain peptides at a point between the hinge region and the disulfide bond connecting the heavy and light chains. The resulting fragment, referred to as an Fab, is monovalent with respect to its antigen-binding site. The Fab fragment retains an entire light chain, as well as one-half of a heavy chain, with both chains covalently linked by the carboxy terminal disulfide bond.

Inbar et al., [4] used a mouse IgA-myeloma protein (MOPC315) to demonstrate that an Fab fragment could be further cleaved by pepsin digestion, to yield an even smaller antigen binding fragment. This fragment, referred to as an Fv, has an approximate molecular weight of 25,000 daltons and is composed of the amino terminal variable regions of the heavy and light chains (V_H and V_L, respectively) held together by non-covalent bonds. The Fv fragment was shown to retain the same binding specificity for 2,4-dinitrophenyl (DNP) as well as the same affinity (Kd=4× 10^{-7}M) as the intact antibody.

Efficient production of antibody fragments in bacteria would appear to be less difficult for Fvs than for the larger fragments or for complete antibodies. Protein refolding is simplified since each active V_H or V_L chain is required to form a single globular domain stabilized by one intrachain disulfide bond. The association of the two chains in an active Fv requires noncovalent interactions only and occurs with a Kd greater than 10^{-8} M for MOPC315 Fv [5].

The work of Hochman et al. [5] predicts that it should be possible to recombine separately expressed MOPC315 V_H and V_L chains to form active Fv molecules in an efficient manner. They used purified MOPC315 Fv, denatured in 8M urea, to isolate individual V_H and V_L chains by DEAE-cellulose chromatography [6]. The inactive V_H and V_L chain components were recombined to form an active Fv following a simple and efficient (80–90% recovery) refolding procedure. In addition, it was shown that active Fv could be recovered efficiently from reduced as well as denatured material [5]. Since it can be anticipated that reduction as well as denaturation will be required to solubilize and purify overexpressed proteins from *E. coli,* it is useful to note that neither reduction nor denaturation of native MOPC315 V_H and V_L chains prior to refolding prevented efficient recoveries of the native Fv [5].

The results of these early experiments were encouraging to the extent that they confirmed the possibility of producing recombinant antibody molecules in *E. coli.* Clearly, however, the low levels of expression in combination with low yields of active material indicated that further efforts would be required for efficient bacterial production of antigen-binding proteins.

Bicistronic Constructs: As a result of the inherent difficulties in recovering active whole antibody chains from *E. coli,* efforts were directed towards the microbial expression and recovery of active Fv or Fab antibody fragments. Success in these efforts was achieved both in yeast and in bacteria. Recovery of active antibody Fv fragments from *E. coli* has since been reported using several different strategies.

Initial success was achieved by two separate groups who reported the recovery of secreted active antibody fragments

from *E. coli* by co-expressing the two chains of either an Fv [7] or an Fab [8] on the same plasmid. Both bicistronic constructs were characterized by a joint expression of separate heavy and light chain fragment genes under the direction of a single transcriptional unit. This co-expression allows for the synthesis of approximately stoichiometric amounts of both chains. Translation and refolding of each chain occurs in close proximity to each other within the cell. In addition, each peptide coding region has been engineered for secretion by the addition of an amino terminal bacterial leader sequence, directing the expressed products through the inner membrane to the bacterial periplasm. This membrane translocation mimics the processing of eukaryotic protein into the lumen of the endoplasmic reticuluum (ER), a process which occurs normally during the immunoglobulin assembly process in mammalian B cells [1]. The passage of the recombinant proteins across the *E. coli* membrane was predicted to be functionally analogous to ER transport, facilitating proper refolding and disulfide formation of antibody fragment molecules [7].

Active antigen-binding fragments were, in fact, isolated by both groups either from the periplasm [7] or directly from the culture medium [8]. Skerra and Plückthun used a bicistronic construct in which bacterial signal sequences for outer membrane protein A (ompA) and alkaline phosphatase (phoA) were fused to synthetic genes encoding the V_H and V_L domains of McPC603, an anti-phosphorylcholine (PC) mouse IgA antibody [9]. Expression was driven by an isopropyl-β-D-thiogalactoside (IPTG) inducible lac promot-eroperator. Active Fv fragments could be rapidly purified to homogeneity by phosphorylcholine affinity chromatography of periplasmic fractions. Typical yields were reported to be approximately 0.2 mg of purified Fv fragment per liter of bacterial culture. Measurements of the affinity of the recombinant Fv gave results identical to the corresponding affinity of native McPC603 isolated from mouse ascites (Kd=6–8× 10^{-6}M).

Better et al. [8] reported higher yields (2 mg/L) of active recombinant L6 Fab (a mouse—human chimeric antibody reactive against the human carcinoma cell line C3347) using a *S. typhimurium* araB (ParaB) promoter to drive the expression of a bicistronic construct containing the full-length L6 light chain and the N-terminal half of the L6 heavy chain (a truncated heavy chain of this type is referred to as an Fd), both preceded by a pectate lyase (pelB) bacterial leader sequence. This construct directed active L6 Fab to the extracellular culture medium from which it could be directly purified using sequential cation-exchange chromatography. Subsequently, the same group reported the successful recovery of active L6 whole antibody as well as Fab fragment from yeast [10].

The bicistronic construct with bacterial leader sequences has since been successfully employed by others, most notably by those involved in the construction of antibody recombinatorial libraries using polymerase chain reaction (PCR) techniques [11–13]. In brief, these libraries are constructed from a large array of individual heavy and light chain fragments, cloned by PCR amplification from a variety of biological sources such as spleen, peripheral blood lymphocyte, and hybridoma cell RNA using antibody-specific generic primers. The heavy and light chain genes are allowed to randomly assort during a subcloning procedure which finally results in the formation of a repertoire of Fab fragments arranged in bicistronic constructs expressed in bacteriophage lambda vectors. These libraries are screened with labeled antigens to identify and isolate novel antibodies. As interesting as this work has been in terms of its potential to replace hybridoma screening for the production of monoclonal antibodies (a somewhat controversial projection, see Winter and Milstein, 1991 [14]), no data has as yet been presented which demonstrates production of either recombinant active Fv or Fab in *E. coli* in significantly high yields using a bicistronic system.

Single-chain constructs: Architects of single-chain constructs have taken the bicistronic approach to the bacterial expression of antibody fragments one step further by expressing tandemly linked VH and VL genes together as a single protein. This work was pioneered by two separate groups [15, 16] using a similar system, which employs a 15–20 amino acid, neutral peptide linker to fuse the carboxy terminus of a V_H or a V_L gene to the N-terminus of its corresponding partner (see FIG. **20**); the order of the two genes appears to be reversible. Bird et al. [16] used a series of custom designed linker sequences based on protein modeling of their projected single-chain Fvs (sFv) while Huston et al. [15] designed a more generic (Gly4, Ser)3 linker which has since been used extensively by other researchers. Both groups used standard *E. coli* promoter/operator (P/O) systems such as the hybrid, lambda leftward operator/rightward promoter (OL/PR) [16] or the tryptophan P/O [15] to drive the expression of sFv proteins in bacteria. Reported recoveries of active sFv protein were good, ranging from 5–30% of expressed protein for an anti-bovine growth hormone (BGH) sFv [16] to 13% for an anti-digoxin sFv [15].

The anti-digoxin sFv yields were later optimized to 23% and then the basic construct was modified by the N-terminal addition of the coding region for fragment B of staphylococcal protein A which binds to the Fc region of IgG [17]. The resulting bifunctional molecule (FB-sFv) was recovered at very high efficiencies (46%) and was shown to crosslink IgG to digoxin-bovine serum albumin. The successful addition of an effector domain to the amino terminus of an immunoglobulin binding region was entirely novel and has since been repeated with other Ab fragments [18–20].

Fusion of a toxin gene to the carboxy terminal end of an sFv has been reported by Chaudhary et al. [18]. The initial immunotoxin construct joined a sFv specific for the interleukin-2 receptor (anti-Tac) to a fragment of the Pseudomonas exotoxin (PE40) from which the native exotoxin binding domain was removed. The anti-Tac sFv was constructed using a $(Gly4, Ser)_3$ linker and expression of the immunotoxin was driven by the strong IPTG-inducible polymerase-specific T7 promoter [21, 22]. The resulting purified and refolded fusion protein (recovered at 0.2 mg/L) was shown to be highly cytotoxic to IL-2 receptor-bearing human cell lines but not to receptor-negative cells. This group has also reported the successful construction of several new single-chain immunotoxin proteins including one in which the coding region for a truncated form of diptheria toxin (DT) is linked to the N-terminus of the anti-Tac sFv [18]. The DT-anti-Tac sFv was shown to be as active as its anti-Tac-PE40 sFv counterpart and was recovered at significantly higher levels (3–5 mg/L).

Higher levels of recovery (10–12 mg/L, or 20% recovery) of active single-chain Ab have been reported by other researchers using the T7 promoter and a $(Gly4\ Ser)_3$ linker to express a sFv specific to the major cellular receptor for human rhinovirus (ICAM-1) [23]. In general, recoveries of active protein from recombinant single-chain Abs (when reported) remain at or below 10 mg/L levels. It is not clear yet whether the apparent limit on recovery levels of most single-chain proteins is a reflection of the level of gene expression, the result of simple peptide to peptide variability, or the inherent limitations imposed by the complexity of sFv refolding.

Separate chain constructs: The expression of V_L and V_H chains in separate bacterial cell lines followed by recombination of purified peptides to form active Fv, is an alternate approach to either the bicistronic or single-chain strategies. Recombinant V_L and V_H peptides can be independently purified, recombined and refolded in vitro in a potentially efficient manner as predicted by the work on native MOPC315 Fv by Hochman et al. [6]. One major advantage of this method of Fv production includes the prospect of high levels of V_H and V_L peptide expression using T7 promoters. In addition, the refolding problem for each separate chain is relatively simple. It is necessary to form only one disulfide bond in a single globular domain. Bond formation in separate chains can be controlled by adjusting protein concentrations downwards during oxidation in order to form only the correct intrachain disulfide bonds. It may be possible with a combination of high levels of protein expression and enhanced refolding efficiencies to greatly reduce the effect of peptide variability on general recoveries of active Fvs.

The first report of active Fv fragments produced by separate chain expression in *E. coli* was included in an international patent application filed in 1988 [24]. These workers obtained moderately high levels of expression (20–140 mg/L) of mouse immunoglobulin light and heavy chain variable region peptides using an inducible tryptophan promoter/operator in protease deficient host cell lines [24]. Active Fv fragment specific for a hen egg lysozyme epitope (Gloop2) was recovered at 2% levels following partial purification and subsequent refolding of V_H and V_L peptides.

Baldwin and Schultz [25] have reported recovery of DNP-binding activity from a chimeric MOPC315 Fv using recombinant V_L peptides associated with native V_H protein. Moderate levels of V_L expression (10–30 mg/L) were obtained in the form of a V_L fusion protein. The MOPC315 V_L coding sequence was linked via a factor Xa recognition site to the bacteriophage lambda CII protein with expression being driven by the lambda leftward promoter. The yield of V_L protein following factor Xa cleavage and purification was between 5–20% and this purified V_L was efficiently refolded in the presence of native V_H yielding active Fv at between 20–30% efficiencies. Overall yields of active MOPC315 recombinant Fv from starting material (V_L fusion protein) are therefore calculated to be between 1–6%.

Cheadle et al. [26] reported the cloning and expression of both the V_H and V_L of MOPC315 in *E. coli* using a bacteriophage T7 promoter sequence. The recombinant chains were initially recovered as inclusion bodies and then dissolved separately in 8M urea, combined together, and refolded by subsequent chaotrope removal. Biologically active Fv was affinity purified from the chain mixture by specific binding to DNP-Lysine Sepharose. Yields of active material as high as 20% were obtained with activity confirmed by fluorescence quench analysis. The purified recombinant Fv displayed a binding affinity identical to the native Fv.

Chimeric Fvs specific for 5-dimethylaminonapthalene-1-sulfonyl (Dns) have been produced using bacterially expressed VH peptides recombined with entire native light (L) chains (44). The V_H chains were produced at surprisingly low levels (10 mg/L) using a T7 promoter in a T7 polymerase transient infection system (lambda phage derivative CE6 [27]). The transient T7 expression system is primarily used when the gene product has been demonstrated to be toxic to host cell growth. Purified V_H was recombined with native homologous light chains and active VHL dimers were recovered with efficiencies between 1–6%.

SUMMARY OF THE INVENTION

The present invention provides for novel hybridoma cell lines, ATCC HB 9763 and 9764, each of which provides as a component of the supernatant of its growth the highly specific monoclonal antibody, 96 and 108, respectively. Cell lines ATCC HB 9763 and 9764 were deposited in the American Type Culture Collection, 12301 Parklawn Drive, Rockville, Md. 20852, a recognized public depository for strains of microorganisms on Jul. 25, 1988. The present invention provides cell lines to produce novel monoclonal antibodies which inhibit the growth of human tumor cells that express human EGF receptor by binding specifically to the EGF receptor found on the cell membrane of the tumor cells.

An object of this invention is to provide two cell lines, each of which produces a novel monoclonal antibody that inhibits the growth of human tumor cells by the antibody binding to the extra-cellular domain of the human EGF receptors of the tumor cells in an antigen-antibody complex, wherein the tumor cells are characterized by their expression of human EGF receptors and mitogenic stimulation by EGF. The monoclonal antibodies are further characterized by their capability to inhibit the growth of either human oral epidermoid carcinoma (KB) cells or human mammary epithelial (184) cells by binding to the extra-cellular domain of the human EGF receptor of the KB or 184 cells in an antigen-antibody complex.

A further object of the invention is to provide a method for inhibiting the growth of human tumor cells that express human EGF receptors and are mitogenically stimulated by human EGF comprising administering an effective amount of a monoclonal antibody to a human cancer patient having said tumor cells whereby the antibody binds to the extracellular domain of the human EGF receptor of the tumor cell in an antigen-antibody complex, and the monoclonal antibody being further characterized by its capability of inhibiting the growth of either 184 or KB cells.

The invention further comprises a therapeutic composition comprising a pharmaceutical carrier in association with an effective amount of either one of the novel monoclonal antibodies to inhibit the growth of human tumor cells that express human EGF receptors and are mitogenically stimulated by human EGF.

Applicant has also surprisingly discovered that the combined treatment of one of the novel monoclonal antibodies with anti-neoplastic drugs such as doxorubicin or cisplatin provides a more efficient treatment for inhibiting the growth of human cancer cells that express human EGF receptors and are mitogenically stimulated by human EGF than the use of the novel monoclonal antibody or the anti-neoplastic agent by itself. The combined treatment using applicant's novel monoclonal antibodies is advantageous because it combines two anti-cancer agents, each operating via a different mechanism of action to yield a cytotoxic response to human tumor cells. That approach could solve problems arising in the clinic, such as, on the one hand, the development of resistance to drugs, and on the other hand, a change in the antigenicity of the tumor cells that would render them unreactive with the antibody. Furthermore, applicant has also surprisingly discovered that the anti-neoplastic agent can be administered at levels substantially lower than the levels required when administering the antineoplastic agent by itself, which are toxic or sub-toxic to the patient. Anti-neoplastic agents other than doxorubicin or cisplatin such as bleomycin sulfate, carmustine, chlorambucil, and cyclophosphamide hydroxyurea may also be used with the novel

monoclonal antibody. The aforementioned list is merely exemplary and is not intended to limit the scope of the invention.

Thus, a further object of this invention provides a method for inhibiting the growth of human tumor cells that express human EGF receptors and are mitogenically stimulated by human EGF comprising administering an effective amount of an anti-neoplastic agent and an effective amount of either one of the novel monoclonal antibodies to a human cancer patient having said tumor cells, whereby the antibody binds to the extra-cellular domain of the human EGF receptor of the tumor cell in an antigen-antibody complex.

A further object of this invention provides a therapeutic composition comprising an effective amount of either one of the novel monoclonal antibodies and anti-neoplastic agent to inhibit the growth of human tumor cells that express human EGF receptors and are mitogenically stimulated by human EGF in association with a pharmaceutical carrier.

BRIEF DESCRIPTION OF THE DRAWINGS

A more complete appreciation of the present invention and many of the attendant advantages thereof will be readily obtained as the invention becomes better understood by reference to the following detailed description in connection with the accompanying drawings. This description is not to be construed as specifically limiting the invention and such variations which would be within the purview of one skilled in this art are to be considered to fall within the scope of this invention.

FIG. 1 demonstrates antitumor activity of 108 mAb in combination with doxorubicin against KB cells implanted subcutaneously. Four doses of 0.45 mg of 108 monoclonal antibody and 37.5 μg of adriamycin were given 24 hours after the tumor injection and repeated 3 times at 3–4 day intervals.

FIG. 2 demonstrates antitumor activity of 108 mAb in combination with cisplatin against KB cells implanted subcutaneously. In FIG. **10** one treatment comprising 1.8 mg 108 monoclonal antibody and 100 μg cisplatin was administered.

FIG. 3 demonstrates antitumor activity of 108 mAb in combination with cisplatin against KB cells implanted subcutaneously. In FIG. **11** mice were treated intravenously a single time, 20 hours after the tumor implantation with 1.9 mg of 108 monoclonal antibody and 0.1 mg cisplatin (Abic, Ramat-Gan, Israel). Each of the substances were separately injected, PBS (●), monoclonal antibody (Δ), cisplatin (□), and monoclonal antibody+cisplatin (◆).

FIG. 4 demonstrates aEGFR inhibition of anchorage dependent cell growth. 184AIN4 (FIG. 4A and FIG. 4B) and MDA-468 (FIG. 4C and FIG. 4D) cells were passed (5,000/well) into triplicate wells of 24-well plates and allowed to attach before antibody was added. 184AIN4 growth media contained 1 ng/ml EGF. Growth media was changed after 48 hours and the cells were counted after 4 days. Data is % control cell numbers (mean±SD). 96 IgM(●—●), 42 IgM (○—○), nonspecific IgM(Δ—Δ), 225 IgG(□—□), 108 IgG (□—□), non-specific IgG(Δ—Δ).

FIG. 5 demonstrates inhibition of 184AIN4-T colony formation by monoclonal aEGFR. Cells were grown in soft agar as described in Example VIII(B) in the presence of 20 nM aEGFR or 20 nM nonspecific antibodies and increasing concentrations of EGF. Data are mean (±SD) number of colonies greater than 60 μM. FIG. 5A). IgG:225 IgG(●—●), 108 IgG(○—○), non-specific IgG(Δ—Δ). FIG. 5B) IgM: 96 IgM (○—○), 42 IgM(●—●), nonspecific IgM(Δ—Δ).

FIG. 6 demonstrates the effects of aEGFR on MDA-468 colony formation. Cells were grown in soft agar as described in Example VIII(C) in the presence of 20 nM aEGFR or nonspecific antibody and increasing concentrations of EGF. Cells were also grown in the presence of EGF alone. Data are mean (±SD) number of colonies greater than 60 μM. FIG. 6A) IgG: 225 IgG(●—●), 108 IgG(Δ—Δ), non-specific IgG(Δ—Δ), EGF alone (○—○). FIG. 6B) IgM: 96 IgM(Δ—Δ), 42 IgM(●—574), nonspecific IgM(Δ—Δ), EGF alone(○—○).

FIG. 7 shows a schematic representation of the plasmid DNA and the expressed gene product for a single-chain Fv (sFv) antibody fragment produced in *E. coli*. A standard PBR322 derivative plasmid with an antibiotic resistance gene (amp^r) contains a generic promoter with accompanying ribosomal binding site (PR). The sFv gene construct is joined to the PR region by a translation initiation codon placed immediately upstream of the native V_H coding sequence. The expressed sFv gene produces a single polypeptide chain in which the carboxyl terminus of the V_H domain is joined to the amino terminus of the V_L domain through a 15 amino acid linker. This linker, as shown in the construct, consists of a (Gly4, Ser)3 repeat sequence (15).

FIG. 8 shows a schematic diagram of the 108 and 96 recombinant V_L and V_H expression constructs. Nucleotide sequence at the 5' and 3' ends of the coding region of each of the constructs is shown, indicating the restriction endonuclease cleavage sites used to clone into pET8c(Km^R). The translation initiation and termination codons flanking the mature V_H and V_L coding regions also are shown.

FIG. 9 shows the nucleotide sequence of 108 V_H cDNA. Codons 1–121 of the variable region of the heavy chain are shown. Underlined areas indicate the three complementary determining regions (CDR) of 108 V_H.

FIG. **10** shows the nucleotide sequence of 108 V_L cDNA. Codons 1–108 of the variable region of the light chain are shown as well as five residues of the constant region. Boxed areas indicate the three complementary determining regions (CDR) of 108 V_L.

FIG. **11** shows the nucleotide sequence of 96 V_H cDNA. Codons 1–118 of the variable region of the heavy chain are shown. Underlined areas indicate the three complementary determining regions (CDR) of 96 V_H.

FIG. **12** shows the nucleotide sequence of 96 V_L cDNA. Codons 1–112 of the variable region of the light chain are shown as well as the first five residues of the constant region. Boxed areas indicate the three complementary determining regions (CDR) of 96 V_L.

Lane 2: Cell lysate 4 hours after IPTG induction. Lane 3: Inclusion Bodies in 6M Guanidine HCl. Lane 4: Material prepared by gel filtration chromatography on Sephacryl S-200 in 6M Guanidine HCl and 1 mM β-mercaptoethanol.

FIG. **13** shows a schematic representation of the renaturation of antibody Fv from denaturant. Starting from the left of the diagram, oxidation of the individual V_H and V_L chains takes place in the presence of denaturant. Refolding takes place following the removal of chaotrope and its replacement with PBS (buffer). Properly refolded V_H and V_L chains reassociate to form an active Fv complex capable of binding ligand. Incorrectly refolded chains form increasingly insoluble aggregates (agg).

FIGS. **14, 15** and **16** demonstrate the inhibition of mAb96 and EGF binding by the recombinant mAb 96 (rFv). FIG. **14**. Positive control showing inhibition of ^{125}I mAb96 binding by unlabelled mAb96. FIG. **15**. Inhibition of ^{125}I mAb96 binding by unpurified 96 Fv. FIG. **16**. Inhibition of

^{125}I-EGF binding by unpurified 96 Fv. For A and B, A431 cells were preincubated either with mAb 96 or with 96 rFv for 30 minutes at 4° C., and the radioligand was allowed to bind for 90 minutes at 4° C. For FIG. 16, cells were preincubated with 96 rFv for 90 minutes before the addition of radiolabelled EGF. 96 rFv was prepared as follows: 10 mg of each chain (V_H and V_L in 8M urea were mixed, rapidly diluted to 30 μg/ml, and then concentrated in a stirred cell apparatus. Insoluble material was discarded. Approximately 5% of the final unpurified material is correctly refolded 96 rFv.

DETAILED DESCRIPTION OF THE INVENTION

EXAMPLE I

Production of Monoclonal Antibodies

A. Immunization and Somatic Cell Hybridization

Balb/c mice were immunized by intraperitioneal injections of CH 71 cells or CH 71 cell membrane preparation. CH 71 cells are Chinese hamster ovary cells which have been transfected with a plasmid bearing a truncated form (deletion of most of the intracellular domain of the EGF-R) of the EGF-R cDNA (Livneh et al., *J. Biol. Chem.*, Vol. 260, 12490 (1986). These transfected cells express approximately 10^6 mutant EGF-R molecules/cell. The choice of CH-71 cells allows the selection in the first screening test of only hybridomas secreting antibodies against the extracellular domain of the EGF-R and avoids the selection of antibodies directed against the human specific carbohydrates linked to the human EGF-R molecule.

The mice were immunized three times on day 0, 13, and 32. The two best responding mice were each boosted by three intraperitioneal injections of CH 71 cells three consecutive days before the fusion. On day 65, the spleen cells of the mice were then fused with NS1 myeloma cells (ratio 5/1) according to the general procedure of Kohler and Milstein, using PEG 4000 (Merck) as the fusing agent. (Kohler and Milstein, Eur. J. Immuno., Vol. 6, 511–519 (1976).

B. Selection and Growth of Hybridoma

The fusion product was diluted in hypoxanthineazaserine (HA) selection medium (G. Buttin et al., Current Topics In Microbiology and Immunology, Vol. 81, 27–36, (1978)) instead of the hypoxanthine-amminopterin-thymidine (HAT) selection medium and distributed in 96 well plates.

The presence of specific antibodies in the medium of the wells of the growing hybridoma cells was first assayed by radioimmunoassay. Cells expressing or not expressing the EGF receptor were plated in 96 well plates. At confluency, they were washed once with binding medium (DMEM, 20 mM Hepes, 0.2 BSA) and incubated for 90 minutes at room temperature with 100 μl of culture supernatant from the different growing hybridomas. Cells were then washed 3 times with binding medium and incubated for a further 60 minutes at room temperature with 100 μl of a solution of iodinated goat antimouse immunoglobulins (250,000 cpm/100 μl.). After 3 washes with PBS (phosphate buffered saline, pH 7.5), the cells were scraped from the wells and the radioactivity which was associated with their surface was counted using a gamma counter. The ability of the antibodies to bind specifically to the surface of cells expressing the EGF receptor (A 431, human fibroblasts or mouse 3T3 cells transfected with human EGF-R DNA constructs) was measured in this way and compared to their ability to bind to cells that do not express the EGF-R (a particular clone of mouse 3T3 cells). The positive hybridomas were cloned by limiting dilution and further tested by measuring their ability to immunoprecipitate ^{35}S methionine or ^{32}P labeled EGF-R from lysates of cell lines of different species (human, mouse, chicken). For this, goat antimouse immunoglobulins were bound to protein A Sepharose by incubation of goat antimouse antibody solution with protein A Sepharose beads for 30 minutes at room temperature. This was followed by washing 3 times with Hepes 20 mM, pH 7.4. Then the goat mouse Igs coated protein A sepharose beads were further incubated for 30 minutes at room temperature with the culture supernatant of the hybridomas, washed 3 times with HNTG buffer (Hepes 20 mM, 150 mM, NaCl, 0.1% Tritonx 100, 10% Glycerol) and incubated for 1 hour at 4 degrees C. with the different cell lysates obtained by lysing cell monolayers with solubilization buffer (1% Tritonx100, 150 mM NaCl, 20 mM Hepes, 1.5 mM EGTA, 1.5 mM $MgCl_2$, 10% Glycerol, Aprotinin, leupeptin and PMSF as protease inhibitors) and centrifugation of the lysate to discard the nuclear pellet. For ^{32}p labeling, the immunoprecipitates were washed with HNTG 3 times and then incubated for 15 minutes with a ^{32}P ATP solution (HNTG with 5 mM $MnCl_2$ and 3 μCi/sample of ^{32}P ATP). Electrophoresis sample buffer was then added and the samples boiled for 10 min at 95 degrees C. prior to loading on a 7.5% SDS polyacrylamide gel. Monoclonal antibodies 108, 96 and 42 were all found to be specific for the human EGF-R. These antibodies were also tested for their ability to inhibit the binding of iodinated EGF to the surface of cells expressing EGF-R. These 3 antibodies inhibit the binding of EGF to its receptor, but the level of inhibition varied with 96>108>42.

EXAMPLE II

Culturing of Cell Lines

A. Culturing of Human Oral Epidermoid Carcinoma Cells (KB Cells)

The KB human tumor cell line derived from oral epidermoid carcinoma was obtained from the American Type Tissue Culture Collection. The cells were grown in Dulbecco's modified Eagle's medium supplemented with 10% fetal calf serum depleted of complement activity by incubation at 56° C. for 30 minutes and grown in glutamine, penicillin, streptomycin and sodium pyruvate, at 37° C. in 5% CO_2: 95% air atmosphere.

B. Culturing of Human Mammary Epithelial Cells (184 Cells) and Human Breast Cancer Cells (MDA-468 Cells)

184AIN4 and 184AIN4-T human mammary epithelial cells were provided by Martha Stampfer, Lawrence Berkeley Laboratory, Berkeley, Calif. 184AIN4 cells were maintained at 37 C. in 5% CO2 and IMEM supplemented with glutamine (0.6 mg/ml), fetal calf serum (0.5%), hydrocortisone (0.5 μg/ml), insulin (5 μg/ml) and EGF (10 ng/ml). 184AIN4-T were maintained at 37 C. in 5% CO2 in IMEM (Biofluids, Rockville, Md.) supplemented with glutamine (0.6 mg/ml), gentamicin (40 mg/ml) and 10% fetal calf serum. MDA-468 cells were cultured under the same conditions and medium as 184 AIN4-T cells.

C. Culturing of 96 IgM and 108 IgG2a Hybridoma Cell Lines

The 108 IgG2a hybridoma cell line was generated by immunizing mice with CH 71 cells expressing the EGF

receptor and cultured under the same conditions as the KB cell line. The 96 IgM hybridoma cell line was generated by the same procedure as that described for the 108 IgG2a hybridoma cell line.

EXAMPLE III

A. Purification of 108 Monoclonal Antibodies from Animals

Ascites from animals injected with the 108 IgG2a hybridoma cells were clarified by centrifugation in an Eppendorf centrifuge at 4° C. for 10 min. Monoclonal antibodies were precipitated by slow addition of saturated ammonium sulfate at 4° C. to a final concentration of 45% (v/v), pH 7.5, for 24 hours. The precipitate was collected by centrifugation at 10,000 g for 15 minutes and washed twice with 50% v/v ammonium sulfate, pH 7.5. at 4° C. Further purification was carried out by affinity chromatography on Sepharose CL protein A (Pharmacia) in 0.14M Tris buffer, pH 8.0 and the 108 monoclonal antibody was eluted with 0.1M citrate buffer, pH 3.0, followed by extensive dialysis against PBS.

B. Purification of 96 Monoclonal Antibodies from Animals

Ascites from animals injected with the 96 IgM hybridoma cells were clarified by centrifugation in a low speed centrifuge at 3000 RPM for 15 minutes, at 4° C. Monoclonal antibodies were precipitated by slow addition of saturated ammonium sulfate at 4° C. to a final concentration of 45% (v/v), pH 7.5, for 24 hours. The precipitate was collected by centrifugation at 10,000 g for 15 minutes and washed twice with 50% v/v ammonium sulfate, pH 7.5 at 4° C. The precipitate was then dissolved in and dialyzed extensively against 50 mM TRIS, pH 8, 0.5 M NaCl. This material was semi-purified by gel filtration using Sephacryl S-3000 equilibrated in 50 mM TRIS, pH 7.8, NaCl 0.5 M. The peak containing the mAb96 antibody was pooled and dialyzed against PBS.

EXAMPLE IV

Purification, Specific Activity and Immunoreactivity of F (ab)'$_2$, and F(ab)' Fragment of 108 Monoclonal Antibody

108 monoclonal antibody (5 mg/ml) in 0.1M sodium-acetate buffer at pH 3.9 was digested in the presence of 4% w/w pepsin (Worthington Biochemical Corporation, New Jersey) for 7 hours at 37° C. Digestion was terminated by adjusting the pH to 8.0 with 2M Tris, followed by dialysis against PBS at 4° C. Remaining intact IgG molecules were removed by protein A affinity chromatography. The Fc portion and smaller fragments were removed by gel filtration on Sepharose G-100. For the preparation of monovalent Fab' fragment, the F(ab)'$_2$ (2 mg/ml) was reduced by 10 mM dithiothreitol in 20 mM Tris buffer, pH 8.2, for 1 hour at 37° C. Alkylation was performed in 40 mM iodoacetamide for 30 minutes at 37° C., followed by extensive dialysis against PBS at 4° C. Purity and complete digestion of the various fragments were analyzed by sodium dodecylsulfate polyacrylamide gel electrophoresis (SDS-PAGE). ^{125}I-labeling of 108 monoclonal antibody was performed by the chloramine T method (Hunter and Greenwood, Preparation of ^{131}Iodine Labeled Human Growth Hormone of High Specific Activity, Nature, Vol. 196, 465–6, (1962)). Specific activities of about 3×10^6 cpm/μg IgG were usually obtained.

The F(ab)'$_2$ and F(ab) fragments of 108 monoclonal antilbody were fully immunoreactive when compared to native intact 108 monoclonal antibody in their capacity to compete with the binding of ^{125}I labeled 108 to EGF receptors exposed on KB cells.

EXAMPLE V

108 Monoclonal Antibody Binding Properties

A. 108 Monoclonal Antibody Binding Activity to Cell Surface EGF Receptors

The antibody binding activity of 108 hybridoma supernatant was determined by an indirect immunofluorescence assay. KB cells (2×10^6 per sample) were trypsinized 24 hours before the assay and placed in test tubes (Falcon, polystyrene round bottom tubes). Prior to assay, the KB cell suspensions were washed with cold PBS and incubated with 108 hybridoma supernatant for 45 min. at 4° C. After washing with PBS containing 1% bovine serum albumin, the cells were incubated with fluorescein labeled rabbit anti-mouse IgG for 45 min. at 4° C. Cell samples were suspended in PBS and analyzed by a fluorescence cell sorter (FACS II, Bectin Dickenson, Mountainview, Calif. U.S.A.).

Uniformity of receptor expression was shown by positive stain in at least 96% of the cells compared with absence of staining observed with supernatant of hybridoma raised against human hepatitis B virus (7HO1). Scatchard analysis of antibody binding parameters at 4° C. revealed an average of 2×10^5 binding sites per cell with KD of 1.8×10^{-9} M^{-1}.

B. A Competitive Radioimmunoassay of Epidermal Growth Factor with 108 Monoclonal Antibody and its Fragments

KB cells (10^5/well in 24 well plates; NUNC) were grown for 24 hours, washed with PBS and incubated with different concentrations of either native antibody or its fragments in DMEM containing 1% bovine serum albumin for 1 hour at 4° C., or at room temperature, in the presence of ^{125}I 108 monoclonal antibody (about 1×10^6 cpm/ml.). The cells were then washed, solubilized in 0.5N NaOH and their radioactivity was determined in a counter (Kontron, Switzerland). Non-specific binding was determined by the addition of 100-fold excess of unlabelled monoclonal antibody. Results are presented as the percentage of radioactivity associated with the cells incubated with unlabelled antibody (intact or fragmented) vs. radioactivity associated with cells incubated without the addition of cold antibody.

EGF competes with the binding of the antibody to the receptor to a maximal level of about 70%.

C. In Vivo Localization of the Radiolabeled 108 Monoclonal Antibody

KB cells (4×10^6) were inoculated subcutaneously on the back of nude mice (5–6 weeks old). After 14 days, when the tumor reached a size of about 1.2 cm. diameter, ^{125}I 108 monoclonal antibody was injected intravenously or intraperitoneally (5×10^6 cpm; 3×10^6 cpm/μg). 7H01 ^{125}I monoclonal antibody to human hepatitis B virus IgG2a served as control. Four days after the administration of antibodies, animals were killed and the radioactivity in the different tissues was determined. Means of at least four animals per group are presented.

Both intravenous and intraperitioneal administration of the tagged 108 monoclonal antibody resulted in antibody concentration at the tumor mass. Administration of control IgG resulted in no concentration at the tumor mass when given intravenously, while a marginal concentration in the

tumor was detected when the antibodies were administered intraperitoneally. The percentage of injected dose accumulated at the tumor mass 96 hours post intravenal injection were 7.8±1.1 and 0.8±0.1 for monoclonal antibody 108 and 7HOI monoclonal antibody (control antibody) respectively, and for the intraperitioneal injection 7.5±0.4 and 1.8±0.2 respectively.

EXAMPLE VI

96 Monoclonal Antibody Binding Properties: A Competitive Radioimmunoassay of Epidermal Growth Factor with 96 Monoclonal Antibody

Washed, confluent MDA-468 cell monolayers in 24-well culture plates were incubated at 4 C. for 2.5 hours with or without various concentrations of antibody or unlabeled EGF in binding buffer (IMEM, 0.1% BSA, 50 mM HEPES)I [^{125}I]EGF (S.A. 80–160 μCi/μg, ICN Radiochemicals, CA) was added for a final concentration of 1 nM. After incubation the monolayers were washed, solubilized with lysis buffer (10 mM Tris, 1 mM EDTA, 0.5% SDS, pH 7.4) and radioactivity was determined using a gamma-counter (LKB-Pharmacia).

All four antibodies were able to inhibit the binding of labeled EGF whereas nonspecific IgG or IgM were ineffective. The two antibodies most effective in inhibiting cell growth (125 IgM and 225 IgG) were also the most effective in inhibiting [^{125}I]EGF binding. These antibodies were able to block [^{125}I]EGF binding to a greater extent than unlabeled EGF.

EXAMPLE VII

Utility of 108 Monoclonal Antibody

A. Colony Inhibition Assay of KB Cells

KB cells were seeded in petri dishes (50×15 mm^2, NUNC) at a concentration of 2×10^2 cells per dish. After 16 to 24 hours medium was replaced with a fresh one containing different concentrations of either native or fragmented 108 monoclonal antibody with or without EGF. On the sixth day cultures were fed with fresh medium containing the above ingredients. On the 15th day the cultures were washed with PBS, fixed with 4% v/v formaldehyde in PBS for 15 min. and stained with hematoxylin. Number of formed colonies (25 cells) was then determined.

Exposure of KB cells to EGF (160 nM) resulted in an increase to 150% in the number of colonies counted 15 days after seeding (14 days after the beginning of the treatment) as compared to cells incubated in the absence of growth factor. In addition EGF caused an increase in the size of KB cell colonies. When a similar experiment was performed in the presence of 108 monoclonal antibody (1.6 μM) the number of cell colonies was reduced to 30% of control values. Moreover, a 100 fold excess of 108 monoclonal antibody added together with EGF given at concentration which caused a 50% increase in the colony number, reduced the number of colonies to 20% of control values. Under the same conditions, F(ab)'$_2$ fragments of 108 monoclonal antibody had no effect on the number of KB colonies. Yet when added in 100-fold excess to EGF, the F(ab)'$_2$ fragments are able to abolish the effect of EGF on the number of formed colonies (from 150% to 103%). Incubation with the same concentration of monoclonal antibody to dinitrophenyl (DNP) did not affect the number of formed colonies.

B. Antitumoral Activity of 108 Monoclonal Antibody and its Fragments in Nude Mice

KB cells (2×10^6) were injected subcutaneously into nude mice, followed by either one or several intravenal injections of the 108 monoclonal antibody, starting one day after tumor cell injection. Tumor parameters were measured twice a week with a caliper and its volume was calculated according to the formula: Tumor volume (mm^3)=lengthxwidthxheight. In order to validate volume measurements, correlation between tumor volume and tumor weight at the day of animal killing was assessed.

The antibody was assayed for its capacity to inhibit the growth of KB cells in nude mice. Animals received 1 mg of either 108 monoclonal antibody or control monoclonal antibody to dinitrophenyl at days 1, 5, 12 and 18 after tumor inoculation. The fragments F(ab)'$_2$ and Fab' were given at antibody equivalent doses. The 108 monoclonal antibody treated group significantly retarded tumor development and growth when compared to the group treated with control monoclonal antibody (P<0017, student-t test). The F(ab)'$_2$, was found to affect tumor growth but less efficiently than the whole antibody (P<0.05 student-t test for days 12, 17, 22, 25). Fab' fragment did not affect the tumor growth. A single 2 mg dose of 108 native monoclonal antibody given one day after injection of tumor cells was found to be as efficient as four treatments of 1 mg given at days 1, 5, 12 and 18 after tumor inoculation. In another experiment, when animals were treated with a single dose of 0.66 mg F(ab)'$_2$ fragments, the antitumoral effect was slightly lower, yet a significant difference between the control and the treated group was found using the Mann Whitney analysis (P<0.03 for days 9, 12, 14, 17) and student-t test (P<0.05 days 9, 12). At the day of sacrifice, tumors were measured and then removed for weight determination. The correlation coefficient between the tumor volume and the tumor weight was 0.95 (P<0.0001).

C. Tumor Growth in the Peritoneal Cavity

The injection of 3×10^6 KB cells intraperitoneally one week after mice (Nude in general background) received x-irradiation (400 rads), brought about the development of an ascitic growth. The intraperitioneal tumor-bearing mice died after 30 days. Three intravenous injections of 108 monoclonal antibody (0.5 mg each) prolonged the life span of animals with 30% of animals not developing tumors at all.

D. Tumor Growth in a Metastatic Form

The metastatic form of the KB tumor could be obtained by the injection of the cells intravenously (iv). Mice injected with, 1.5×10^6 KB cells developed tumor nodules in the lungs 4–6 weeks after their implantation. This tumor model mimics the situation in the clinic, where tumor cells infiltrate into internal organs. This is the major problem in the treatment of cancer. The KB cell injection was followed by 3 intravenous injections of 0.5 mg 108 monoclonal antibody at days 6, 9 and 13 after the tumor cell injection. At the termination of the experiment, the lungs were removed, fixed in formaldehyde, and paraffin embedded. Serial sections were cut 4–5 μm in thickness and stained with hematoxylin. The number of metastatic nodules of various depths through the lungs was obtained by light microscopy analysis. Isolation of three metastatic cell clones from lungs of tumor bearing animals and their assay for receptor levels revealed persistence of receptor expression. Treatment by the antibody reduced the number of lung tumor nodules to 15% of those in the respective controls. (P<0.05 Mann-Whitney analysis).

EXAMPLE VIII

Utility of 96 Monoclonal Antibody

A. 96 Inhibits 184A1N4 and MDA-468 Cell Growth

184AIN4 and MDA-468 cells were passed (5,000/well) into triplicate wells of 24-well plates and allowed to attach

before antibody was added. 184AIN4 growth media contained 1 ng/ml EGF and differing amounts of EGFR antibody which was added to the growth media simultaneously with the EGF. MDA 468 growth media contained no EGF. Growth media was changed after 48 hours and the cells were counted after 4 days. At the end of the experimental growth period cells were harvested with trypsin-EDTA and counted using a Particle Data cell counter (Particle Data, Inc., Elmhurst, Ill.). Data is % control cell numbers (mean±SD). 96 IgM(●—●), 42 IgM(o—o), nonspecific IgM(Δ—Δ), 225 IgG(□—□), 108 IgG(□—□), non-specific IgG (Δ—Δ). (See FIGS. 4A–4D)

B. 96 Colony Inhibition Assay of 184AIN4 Cells

184AIN4-T cells were suspended in semisolid agar medium containing 0.4% Bacto-Agar (Difco, Detroit, Mich.), IMEM,10% FBS and treatments. Cells were plated (10,000/dish) into triplicate 35 nM culture dishes containing 1 ml IMEM, 0.6% agar and 10% FBS. The dishes were incubated for 10–14 days at 37 C. in 5% CO in the presence of 20 nM aEGFR or 20 nM nonspecific antibodies and increasing concentrations of EGF. Data are mean (±SD) number of colonies greater than 60 μM. A) IgG:225 IgG (●—●), 108 IgG (o—o), non specific IgG (Δ—Δ). B) IgM: 96 IgM (o—o), 42 IgM (●—●), nonspecific IgM (Δ—Δ). Cell colonies larger than 60 um in diameter were counted using a Bausch & Lomb colony counter (See FIGS. 5A–5B).

C. 96 Colony Inhibition Assay of MDA-468 Cells

MDA-468 cells were suspended in semisolid agar medium containing 0.4% Bacto-Agar (Difco, Detroit, Mich.) IMEM, 10% FBS and treatments. Cells were plated (10,000/dish) into triplicate 35 mm culture dishes containing 1 ml IMEM, 0.6% agar and 10% FBS. The dishes were incubated for 10–14 days at 37 C. in 5% C02 in the presence of 20 nM aEGFR or 20 nM nonspecific antibodies and increasing concentrations of EGF. Data are mean (±SD) number of colonies greater than 60 um. A) IgG:225 IgG (●—●) 108 IgG (Δ—Δ) non-specific IgG (Δ—Δ), EGF alone (o—o). B) IgM: 96 IgM (Δ—Δ), 42 IgM(●—●) nonspecific IgM (Δ—Δ) EGF alone (o—o). Cell colonies larger than 60 nM in diameter were counted using a Bausch & Lomb colony counter. (See FIGS. 6A–6B)

EXAMPLE IX

Utility of 108 Monoclonal Antibody

A. Administered with Doxorubicin

Monoclonal antibody 108 were injected to form a subcutaneous tumor. Four doses of 0.45 mg of 108 monoclonal antibody and 37.5 μg of doxorubicin (adriamycin) were given 24 hours after the tumor injection and repeated 3 times at 3–4 day intervals. The volume of the tumor was compared to the controls: phosphate buffered saline antibody alone or drug alone. (See FIG. 1.)

B. Administered with Cisplatin

a) A single treatment comprising 1.8 mg 108 monoclonal antibody and 100 μg cisplatin was administered twenty four hours after the subcutaneous tumor inoculation with 2×10^6 KB cells. The results are presented in FIG. 2.

b) A single treatment comprising 1.9 mg 108 monoclonal antibody and 0.1 μg cisplatin were injected intravenously each in a separate needle 20 hours after the tumor transplantation. The combined treatment was significantly better than each of the treatments alone ($P<0.02$ by student-t-test, $P<0.007$ by Mann Whitney analysis, FIG. 3).

EXAMPLE X

Expression and Recombination of Separate Chain Constructs of 96 and 108 V_L and V_H Chains

A. *E. coli* Strains and Plasmids

E. coli strain BL21 (DE3) and the plasmid expression vector pET8c were kindly provided by Dr. F. W. Studier of Brookhaven National Laboratories. This plasmid contains a fragment of T7 DNA specifying the gene 10 promoter inserted into the BamHI site of pBR322 so as to direct transcription counterclockwise. This plasmid also provides a transcription terminator for T7 RNA polymerase, a ribosome binding site and an ATG for translation initiation, with the ATG overlapping an Ncol restriction site (CCATGG).

The plasmid pET8c (Km^R)was also received from Dr. Studier and was constructed by removing the ampicillin resistance gene from pET-8c [21, 22, 27] via excision of a BspHI-EcoRI fragment (pBR322 bp 3195–4361) and replacing it with an 869 bp fragment encoding kanamycin resistance (Km^R), with the Km^R gene oriented clockwise in the vector. The Km^R gene derives from Tn903 [28] and was obtained using the polymerase chain reaction with pUC4KISS [29] as template. The fragment carrying the Km^R gene starts 50 nucleotides ahead of the Km^R initiation codon and ends exactly at the termination codon. A Stratagene pBS plasmid DNA (Bluescript II SK+, Stratagene; La Jolla, Calif.) was used as a sub-cloning vector and transformed into commercially available *E. coli* host cell strains such as Invitrogen DH-1 competent cells (Invitrogen, San Diego, Calif.).

B. Oligonucleotides and Chemicals

Oligonucleotides were synthesized on an Applied Biosystems Model 380A synthesizer using the phosphoramidite method. All routine chemicals (e.g. urea, Tris buffer, DNP-lysine etc.) were purchased from standard suppliers such as Sigma (St. Louis, Mo.) and Fisher (Pittsburgh, Pa.). Radioactive chemicals were purchased from New England Nuclear (Boston, Mass.). Restriction and other DNA-modifying enzymes (e.g. T4 DNA ligase, T4 polynucleotide kinase, calf intestinal phosphatase etc.) were purchased from standard biotechnology manufacturers such as New England Biolabs (Beverly, Mass.) and Boehringer Mannheim (Indianapolis, Ind.).

C. Identification of Monoclonal Antibody 108 and 96 cDNA Clones

In order to obtain cDNA clones for both 108 and 96 light and heavy chains, poly (A)-containing RNA was isolated from the respective hybridoma cell lines using standard methods [30]. The first strand cDNA was synthesized using an oligo (dT) primer. The first strand cDNA was then used as a template for second strand synthesis using the method of Gubler and Hoffman [31]. The double stranded cDNA was then treated with EcoRI methylase and DNA polymerase using reaction conditions described in Maniatis [30]. The mixture was then cleaved with EcoRI and fractionated on an 8% polyacrylamide gel. DNA with a size greater than 600 bp was eluted from the gel and then collected by ethanol precipitation. The cDNA was then inserted into EcoRI cleaved and phosphatase treated lambda gt11 DNA using T4

DNA Ligase, to produce a library of approximately one million transformants. Two separate libraries were constructed, one for identifying 108 sequences and the second for identifying 96 sequences. V_H and V_L cDNA clones were identified by hybridization with an oligonucleotide probe specific for the constant region. Insert DNA from positive phage was subcloned into pBS vectors. The DNA sequence for the V_H and V_L coding regions were verified for all V_H and V_L clones selected for further study. DNA sequencing reactions were carried out as per manufacturers instructions (Sequenase, USB; Cleveland, Ohio).

cDNA clones encoding the variable regions of both monoclonal antibody 96 and 108 heavy and light chains were obtained from cDNA libraries constructed from the respective hybridoma cell lines. The nucleotide sequence of all four variable regions is shown in FIGS. 9–12.

D. Construction of Expression Vectors for V_H and V_L cDNA

In order to direct expression of the various V_H and V_L cDNAs they were placed under the control of the bacteriophage T7 promoter[21, 22, 27]. In this system, the cDNA is placed into a vector containing the promoter and translation initiation signals for the TØ protein of bacteriophage T7. T7 RNA polymerase can then be delivered to the host cell by either induction or infection. In the present example the antibody expression vectors were placed into a cell that carries a prophage containing the gene for T7 RNA polymerase under control of the lac UV5 promoter. Addition of the lactose analog IPTG to a growing culture of cells induces T7 RNA polymerase, which in turn transcribes the target DNA in the plasmid. Transcription by T7 RNA polymerase is so active that target RNA can accumulate to amounts comparable to ribosomal RNA and target proteins can constitute the majority of cellular protein.

Plasmids expressing the antibody V_L or V_H sequence and conferring resistance to kanamycin were constructed from pET-8c(Km^R) and PCR products derived from the various cDNAs. Briefly, four oligonucleotides each capable of hybridizing to the 5' of one of the various cDNAs were designed. All four oligonucleotides incorporated an NcoI restriction site. Similarly, four oligonucleotides each capable of hybridizing to the 3' of one of the various cDNAs were also designed. In the latter case all four oligonucleotides incorporated an BamHI restriction site.

Four separate PCR reactions were carried out using the appropriate combination of template DNA (108 V_H or V_L and 96 V_H or V_L) and PCR primers. Following 30 cycles of PCR the various reaction products were digested with NcoI and BamHI and the insert fragment was then ligated to NcoI/BamHI cleaved pET8c(Km^R). The resulting plasmid DNA was then transformed into *E. coli* DH-1 cells and a single isolate from each transformation was identified that released the appropriate size fragment by digestion with NcoI and BamHI. DNA from a positive isolate for each of the four chains was then used to transform *E. coli* BL21 (DE3). A single isolate from each of these transformations was the used for expression of the various chains as described below. A schematic diagram of the expression vector constructs is indicated in FIG. 8.

E. Expression of V_H, V_L, and sFv Genes in *E. coli*

Fresh overnight cultures were diluted 1:100 and grown to an O.D.595 of ~0.4 and then induced with 1 mM isopropyl β-D-thiogalactopyranoside (IPTG). Samples were removed at selected time points, centrifuged and the pellet resuspended in sample buffer (20 mM Tris-HCl pH 6.8, 3.0% SDS, 15% glycerol, 0.1-β-mercaptoethanol, 0.001% bromophenol blue dye) before analysis by SDS gel electrophoresis [32].

Expression vectors containing the various recombinant Fv constructs under the control of the T7 promoter were introduced into BL21 (DE3) cells [21, 22, 27]. This cell line is an *E. coli* lysogen containing a single copy of the gene for T7 RNA polymerase in the chromosome under the control of the IPTG-inducible lac UV-5 promoter. The addition of IPTG to cell cultures elevates the expression levels of T7 RNA polymerase and thus indirectly induces the expression of recombinant proteins under the control of T7 promoters.

F. Protein Purification

The first step in the purification of the individual V_H, V_L, or sFv proteins was their isolation in the form of bacterial inclusion bodies. *E. coli* cell pellets from 500 ml induced cultures (2–4 hours with 1 mM IPTG) were resuspended in 20 ml of 50 mM Tris-HCl, pH 9.0, 2.0% glycerol and 0.1 mM EDTA. This suspension was sonicated 2×15 sec. on ice and then centrifuged at 15,000 g for 20 min. The precipitate (containing essentially all of the V_H, V_L, or sFv proteins) was resuspended in 8 M urea, 50 mM Tris-HCl pH 8.0, sonicated 2×15 sec. on ice, stored overnight at 4° C. and then clarified by centrifugation at 15,000 g for 20 min. Supernatant samples in urea were adjusted to ~1 mg/ml (VH, VL) or ~0.1 mg/ml (sFv), as calculated from absorbance measurements using extinction coefficients $E_{280\ nm\ 1\ cm}^{0.1\%}$=2.0 for V_H, 1.0 for V_L, or 1.5 for Fv (used also to estimate sFv) [6] and stored overnight at 4° C. These samples were either used directly for analysis of refolding and recovery of active Fv or processed for further purification.

V_H, V_L, and sFv proteins purified from bacterial inclusion bodies were solubilized in 6 M Guanidine HCl, 50 mM Tris-HCl pH 8.0, 5 mM EDTA and 1 mM β-mercaptoethanol. Size exclusion chromatography was performed on a Sephacryl S-200 column (3×90 cm). Samples of S-200 purified V_H, V_L, or sFv protein were further treated by ion-exchange chromatography following buffer exchange by dialysis to 8 M urea, 50 mM Tris-HCl pH 8.0, 20 mM NaCl, 0.01 mM β-mercaptoethanol. Samples were passed over a 5 ml Q-Sepharose anion exchange column and eluted with a 0.02–0.5 M NaCl gradient in 8 M Urea, 50 mM Tris-HCl pH 8.0.

Peptides from each of the separate chain constructs (V_H or V_L) and the sFv were found primarily in the form of insoluble inclusion bodies. This finding was consistent for proteins over-expressed in *E. coli* [34] and from a purification standpoint, this sequestration was useful since recombinant proteins were conveniently isolated in a highly enriched form.

V_H, V_L, and sFv proteins exhibited minimal solubility in nondenaturing solvents and, therefore, were dissolved in either 8 M urea or 6 M guanidine hydrochloride (Guanidine HCl). When these chaotropes were removed either slowly by dialysis or rapidly by dilution, V_L remained soluble longer than V_H. However, neither individual chain remained in solution in PBS except at low protein concentration (less than 50 μg/ml). Significantly recombinant V_H and V_L chains did remain in solution in PBS at concentrations up to ~1 mg/ml when later recovered as active Fvs.

Further purification of recombinant V_H, V_L, or sFv proteins isolated in inclusion bodies and solubilized in Guanidine HCl with reduction was performed by size exclusion chromatography. Recoveries of S-200 purified V_H, V_L, and

sFv proteins following size exclusion chromatography varied with different inclusion body preparations and ranged from 100–200 mg/liter.

G. Refolding of V_H, V_L, and sFv Peptides

The refolding of V_H and V_L peptides was carried out by the method of Hochman et al.[18, 33] Equimolar amounts of V_H and V_L proteins were added together in 8 M urea, 50 mM Tris-HCl, pH 8.0, to a final protein concentration of ~1 mg/ml. Refolding was initiated by the removal of chaotrope either by extensive dialysis in PBS or by rapid dilution 20-fold into PBS. Refolded material following rapid dilution (final urea concentration equal to 0.4 M) was maintained at room temperature for a minimum of 30 minutes.

Refolding of sFv protein was preceded by reduction of sFv in 8 M urea, 50 mM Tris-HCl, pH 8.0, at 37° C. for 1 hour with 0.1 M β-mercaptoethanol. Reduction was carried out at protein concentrations of 1 mg/ml and then diluted with the same buffer to 50–100 μg/ml. The diluted sample was then dialyzed extensively, first against 8 M urea, 50 mM Tris-HCl, pH 8.0, and then to final equilibration in PBS.

Recombinant V_H and V_L and sFv peptides expressed to high levels in *E. coli* were found to be, as anticipated, sequestered in insoluble inclusion bodies. As a result, strong denaturants were required for protein solubilization. The recovery of active protein following this treatment was dependent upon the use of an effective in vitro refolding procedure.

In general, protein refolding is initiated by the removal of the solubilizing chaotrope under conditions designed to promote the most effective outcome. FIG. **13** illustrates this general scheme by outlining a simple model of the steps required for protein refolding of an antibody Fv. In this model, oxidation of the individual V_H and V_L chains takes place separately, each in the presence of denaturant. Intrachain disulfide bond formation within the relaxed chains is concentration dependent and the proper formation of these bonds presumably promotes the most effective subsequent refolding. Refolding itself is initiated by the transfer of the combined V_H and V_L protein from denaturant into a physiological buffer (e.g. PBS). Successfully refolded V_H and V_L chains can then associate together to form an active Fv complex capable of specific ligand binding.

A standard procedure for the refolding of recombinant 108 and 96 V_L and V_H was adopted based upon the conditions originally used by Hochman et al. [18, 33] to renature the native MOPC315 V_H and V_L. Solubilized recombinant 108 or 96 V_H and V_L chains (either directly from inclusion bodies or after further purification) were allowed to oxidize in air to greater than 90%. The separate chains were combined in denaturant, diluted 1:20 in PBS, and allowed to refold at room temperature. The refolded chains were then used in the binding experiments described below.

H. Biological Activity

FIGS. **14** and **15** show that in a competition binding experiment, the 96 rFv competed for binding of MAb 96 to A431 cells. Similar results were observed for 108 rFv competing for MAb 108 binding to A431 cells. The 96 rFv also inhibited the binding of radioiodinated EGF to A431 cells, as shown in FIG. **16**.

Antibody fragments may be produced by proteolytic degradation of entire immunoglobulin molecules, or by recombinant expression of DNAs encoding antibody fragments. The antibody fragment 96 Fv does not cause the receptor to dimerize, and does not activate the receptor. The antibody fragment induces internalization of the receptor without inducing its degradation. A toxin, radiochemical, or drug can be attached to the antibody fragment. The use of a variable region antibody fragment directed to a cellular receptor is useful in targeting drug delivery to cells expressing that receptor in order to affect cellular physiology and/or metabolism.

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SEQUENCE LISTING

(1) GENERAL INFORMATION:

(iii) NUMBER OF SEQUENCES: 17

(2) INFORMATION FOR SEQ ID NO:1:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 45 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: other nucleic acid

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:1:

TCCGGAGGCG GTGGCTCGGG CGGTGGCGGC TCGGGTGGCG GCGGC 45

(2) INFORMATION FOR SEQ ID NO:2:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 15 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:2:

Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly
1 5 10 15

(2) INFORMATION FOR SEQ ID NO:3:

-continued

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 12 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: other nucleic acid

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:3:

ACCATGGATG TT 12

(2) INFORMATION FOR SEQ ID NO:4:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 15 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: other nucleic acid

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:4:

GCTGCATGAG GATCC 15

(2) INFORMATION FOR SEQ ID NO:5:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 12 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: other nucleic acid

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:5:

ACCATGGAAG TG 12

(2) INFORMATION FOR SEQ ID NO:6:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 15 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: other nucleic acid

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:6:

TCTGCATGAG GATCC 15

(2) INFORMATION FOR SEQ ID NO:7:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 12 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: other nucleic acid

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:7:

ACCATGGAAA TC 12

(2) INFORMATION FOR SEQ ID NO:8:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 12 base pairs
(B) TYPE: nucleic acid

-continued

(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: other nucleic acid

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:8:

ACCATGCAGG TT 12

(2) INFORMATION FOR SEQ ID NO:9:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 18 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: other nucleic acid

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:9:

TCCTCCTAAT AAGGATCC 18

(2) INFORMATION FOR SEQ ID NO:10:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 363 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(ix) FEATURE:
(A) NAME/KEY: CDS
(B) LOCATION: 1..363

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:10:

```
CAG GTT CAG CTG CAG CAG TCT GGA GCT GAG CTG ATG AAG CCT GGG GCC      48
Gln Val Gln Leu Gln Gln Ser Gly Ala Glu Leu Met Lys Pro Gly Ala
 1               5                  10                  15

TCA GTG AAG ATA TCC TGC AAG GCT ACT GGC TAC ACA TTC AGT AGT TAC      96
Ser Val Lys Ile Ser Cys Lys Ala Thr Gly Tyr Thr Phe Ser Ser Tyr
            20                  25                  30

TGG ATA GAG TGG GTA AAG CAG AGG CCT GGA CAT GGC CTT GAG TGG ATT     144
Trp Ile Glu Trp Val Lys Gln Arg Pro Gly His Gly Leu Glu Trp Ile
        35                  40                  45

GGA GAG ATT TTA CCG GGA AGT AAA AAA ACT AAC TAC AAT GAG AAG TTC     192
Gly Glu Ile Leu Pro Gly Ser Lys Lys Thr Asn Tyr Asn Glu Lys Phe
    50                  55                  60

AAG GGA AAG GCC ACA TTC ACT GCA GAT ACA TCC TCC AAC ACA GCC TAC     240
Lys Gly Lys Ala Thr Phe Thr Ala Asp Thr Ser Ser Asn Thr Ala Tyr
65                  70                  75                  80

ATG CAA TTT AGC AGC CTG ACA TCT GAG GAC TCT GCC GTC TAT TAC TGT     288
Met Gln Phe Ser Ser Leu Thr Ser Glu Asp Ser Ala Val Tyr Tyr Cys
                85                  90                  95

GCA AGA TAT TAC TAT AGG AAC GAC GAC TAT GGT ATG GAC TAC TGG GGT     336
Ala Arg Tyr Tyr Tyr Arg Asn Asp Asp Tyr Gly Met Asp Tyr Trp Gly
            100                 105                 110

CAA GGA ACC TCA GTC ACC GTC TCC TCA                                 363
Gln Gly Thr Ser Val Thr Val Ser Ser
        115                 120
```

(2) INFORMATION FOR SEQ ID NO:11:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 121 amino acids
(B) TYPE: amino acid

-continued

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:11:

```
Gln Val Gln Leu Gln Gln Ser Gly Ala Glu Leu Met Lys Pro Gly Ala
 1               5                  10                  15

Ser Val Lys Ile Ser Cys Lys Ala Thr Gly Tyr Thr Phe Ser Ser Tyr
            20                  25                  30

Trp Ile Glu Trp Val Lys Gln Arg Pro Gly His Gly Leu Glu Trp Ile
        35                  40                  45

Gly Glu Ile Leu Pro Gly Ser Lys Lys Thr Asn Tyr Asn Glu Lys Phe
    50                  55                  60

Lys Gly Lys Ala Thr Phe Thr Ala Asp Thr Ser Ser Asn Thr Ala Tyr
65                  70                  75                  80

Met Gln Phe Ser Ser Leu Thr Ser Glu Asp Ser Ala Val Tyr Tyr Cys
                85                  90                  95

Ala Arg Tyr Tyr Tyr Arg Asn Asp Asp Tyr Gly Met Asp Tyr Trp Gly
            100                 105                 110

Gln Gly Thr Ser Val Thr Val Ser Ser
        115                 120
```

(2) INFORMATION FOR SEQ ID NO:12:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 336 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(ix) FEATURE:
(A) NAME/KEY: CDS
(B) LOCATION: 1..336

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:12:

```
GAA ATC CAC ATG ACA CAG ACT ACA TCC TCC CTG TCT GCC TCT CTG GGA      48
Glu Ile His Met Thr Gln Thr Thr Ser Ser Leu Ser Ala Ser Leu Gly
 1               5                  10                  15

GAC AGA GTC ACC ATC AGT TGC AGT GCA AGT CAG GAC ATC AGG AAT TAT      96
Asp Arg Val Thr Ile Ser Cys Ser Ala Ser Gln Asp Ile Arg Asn Tyr
            20                  25                  30

TTA AAC TGG TAT CAG CAG AAA CCT GAT GGA ACT GTT AAA CTC CTG ATC     144
Leu Asn Trp Tyr Gln Gln Lys Pro Asp Gly Thr Val Lys Leu Leu Ile
        35                  40                  45

TAT TAC ACA TCA ACT TTA CAT TCA GGA GTC CCA TCA AGG TTC AGT GGC     192
Tyr Tyr Thr Ser Thr Leu His Ser Gly Val Pro Ser Arg Phe Ser Gly
    50                  55                  60

AGC GGG TCT GGG ACA GAT TAT TCT CTC ACC ATC AGC AAC CTG GAA CCT     240
Ser Gly Ser Gly Thr Asp Tyr Ser Leu Thr Ile Ser Asn Leu Glu Pro
65                  70                  75                  80

GAA GAT ATT GCC ACT TAT TAT TGT CAG CAG TAT AGT AAG ATT CCG TAC     288
Glu Asp Ile Ala Thr Tyr Tyr Cys Gln Gln Tyr Ser Lys Ile Pro Tyr
                85                  90                  95

ACG TTC ACA GGG GGG ACC AAG CTG GAA ATA AAA CGG GCT GAT GCT GCA     336
Thr Phe Thr Gly Gly Thr Lys Leu Glu Ile Lys Arg Ala Asp Ala Ala
            100                 105                 110
```

(2) INFORMATION FOR SEQ ID NO:13:

(i) SEQUENCE CHARACTERISTICS:

-continued

(A) LENGTH: 112 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:13:

```
Glu Ile His Met Thr Gln Thr Thr Ser Ser Leu Ser Ala Ser Leu Gly
 1               5                  10                  15

Asp Arg Val Thr Ile Ser Cys Ser Ala Ser Gln Asp Ile Arg Asn Tyr
            20                  25                  30

Leu Asn Trp Tyr Gln Gln Lys Pro Asp Gly Thr Val Lys Leu Leu Ile
        35                  40                  45

Tyr Tyr Thr Ser Thr Leu His Ser Gly Val Pro Ser Arg Phe Ser Gly
    50                  55                  60

Ser Gly Ser Gly Thr Asp Tyr Ser Leu Thr Ile Ser Asn Leu Glu Pro
65                  70                  75                  80

Glu Asp Ile Ala Thr Tyr Tyr Cys Gln Gln Tyr Ser Lys Ile Pro Tyr
                85                  90                  95

Thr Phe Thr Gly Gly Thr Lys Leu Glu Ile Lys Arg Ala Asp Ala Ala
            100                 105                 110
```

(2) INFORMATION FOR SEQ ID NO:14:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 354 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(ix) FEATURE:
(A) NAME/KEY: CDS
(B) LOCATION: 1..354

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:14:

```
GAA GTG CAG CTG GTG GAG TCT GGG GGA GGC TTA GTG AGG CCT GGA GGG        48
Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Arg Pro Gly Gly
 1               5                  10                  15

TCC CTG AAA CTC TCC TGT GCA GCC TCT GGA TTC GCT TTC AGT AAC TAT        96
Ser Leu Lys Leu Ser Cys Ala Ala Ser Gly Phe Ala Phe Ser Asn Tyr
            20                  25                  30

GAC ATG TCT TGG GTT CGC CAG ACT CCG GAG AAG AGG CTG GAG TGG GTC       144
Asp Met Ser Trp Val Arg Gln Thr Pro Glu Lys Arg Leu Glu Trp Val
        35                  40                  45

GCG TAC ATT GGT AAT GGT GGT AAC ACC TAC TCT CCA GAC ACT GTG AAG       192
Ala Tyr Ile Gly Asn Gly Gly Asn Thr Tyr Ser Pro Asp Thr Val Lys
    50                  55                  60

GGC CGA TTC ACC ATC TCC AGA GAC AAT GCC GAG AAC ACC CTA TAC CTT       240
Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Glu Asn Thr Leu Tyr Leu
65                  70                  75                  80

CAA ATG AGC AGT CTG AAG TCT GAG GAC ACA GCC ATT TAT TAC TGT GCA       288
Gln Met Ser Ser Leu Lys Ser Glu Asp Thr Ala Ile Tyr Tyr Cys Ala
                85                  90                  95

AGT CAC TAT GGT TAC GAC GGG AGG TTT GCT TAC TGG GGC CAA GGG ACT       336
Ser His Tyr Gly Tyr Asp Gly Arg Phe Ala Tyr Trp Gly Gln Gly Thr
            100                 105                 110

CTG GTC ACT GTC TCT GCA                                              354
Leu Val Thr Val Ser Ala
        115
```

-continued

(2) INFORMATION FOR SEQ ID NO:15:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 118 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:15:

```
Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Arg Pro Gly Gly
 1               5                  10                  15

Ser Leu Lys Leu Ser Cys Ala Ala Ser Gly Phe Ala Phe Ser Asn Tyr
            20                  25                  30

Asp Met Ser Trp Val Arg Gln Thr Pro Glu Lys Arg Leu Glu Trp Val
        35                  40                  45

Ala Tyr Ile Gly Asn Gly Gly Asn Thr Tyr Ser Pro Asp Thr Val Lys
    50                  55                  60

Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Glu Asn Thr Leu Tyr Leu
65                  70                  75                  80

Gln Met Ser Ser Leu Lys Ser Glu Asp Thr Ala Ile Tyr Tyr Cys Ala
                85                  90                  95

Ser His Tyr Gly Tyr Asp Gly Arg Phe Ala Tyr Trp Gly Gln Gly Thr
            100                 105                 110

Leu Val Thr Val Ser Ala
        115
```

(2) INFORMATION FOR SEQ ID NO:16:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 351 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(ix) FEATURE:
(A) NAME/KEY: CDS
(B) LOCATION: 1..351

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:16:

```
GAT GTT GTG ATG ACC CAA AGT CCA CTC TCC CTG CCT GTC AGT CTT GGA       48
Asp Val Val Met Thr Gln Ser Pro Leu Ser Leu Pro Val Ser Leu Gly
 1               5                  10                  15

GAT CAA GCC ACC ATC TCT TGC AGA TCT AGT CAG AGC CTT GAA CAC AGT       96
Asp Gln Ala Thr Ile Ser Cys Arg Ser Ser Gln Ser Leu Glu His Ser
            20                  25                  30

AAT GGA GAC ACC TAT TTA CAT TGG TAC CTG CAG AAG GCA GGC CAG TCT      144
Asn Gly Asp Thr Tyr Leu His Trp Tyr Leu Gln Lys Ala Gly Gln Ser
        35                  40                  45

CCA AAG CTC CTG ATC TAC AAA GTT TCC AAC CGA TTT TCT GGG GTC CCG      192
Pro Lys Leu Leu Ile Tyr Lys Val Ser Asn Arg Phe Ser Gly Val Pro
    50                  55                  60

GAT AGG TTC AGT GGC AGT GGA TCA GGG ACA GAT TTC ACA CTC AAG ATC      240
Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile
65                  70                  75                  80

AGC AGA GTG GAG GCT GAG GAT CTG GGA GTT TAT TTC TGC TGT CAA AGT      288
Ser Arg Val Glu Ala Glu Asp Leu Gly Val Tyr Phe Cys Cys Gln Ser
                85                  90                  95

ACA CAT GTT CCG TGG ACG TTC GGT GGA GGC ACC AAC CTG GAA ATC AAA      336
Thr His Val Pro Trp Thr Phe Gly Gly Gly Thr Asn Leu Glu Ile Lys
            100                 105                 110
```

-continued

```
CGG GCT GAT GCT GCA                                                    351
Arg Ala Asp Ala Ala
       115
```

(2) INFORMATION FOR SEQ ID NO:17:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 117 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:17:

```
Asp Val Val Met Thr Gln Ser Pro Leu Ser Leu Pro Val Ser Leu Gly
 1               5                  10                  15

Asp Gln Ala Thr Ile Ser Cys Arg Ser Ser Gln Ser Leu Glu His Ser
            20                  25                  30

Asn Gly Asp Thr Tyr Leu His Trp Tyr Leu Gln Lys Ala Gly Gln Ser
        35                  40                  45

Pro Lys Leu Leu Ile Tyr Lys Val Ser Asn Arg Phe Ser Gly Val Pro
    50                  55                  60

Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile
65                  70                  75                  80

Ser Arg Val Glu Ala Glu Asp Leu Gly Val Tyr Phe Cys Cys Gln Ser
                85                  90                  95

Thr His Val Pro Trp Thr Phe Gly Gly Gly Thr Asn Leu Glu Ile Lys
            100                 105                 110

Arg Ala Asp Ala Ala
       115
```

What is claimed:

1. A method for inhibiting the growth of human tumor cells that express human EGF receptors and are mitogenically stimulated by EGF, the method comprising administering an effective amount of an anti-neoplastic agent and an effective amount of a monoclonal antibody to a human cancer patient having said tumor cells; (i) wherein said antibody binds to the extra-cellular domain of the human EGF receptor of said tumor cell; (ii) wherein the antibody is not conjugated to the anti-neoplastic agent; and (iii) wherein the antibody inhibit the binding of EGF to the EGF receptor.

2. A method for inhibiting the growth of human tumor cells that express human EGF receptors and are mitogenically stimulated by human EGF according to claim 1 wherein said anti-neoplastic agent is doxorubicin.

3. A method for inhibiting the growth of human tumor cells that express human EGF receptors and are mitogenically stimulated by human EGF according to claim 1 wherein said anti-neoplastic agent is cisplatin.

4. A method for inhibiting the growth of human tumor cells that express human EGF receptors and are mitogenically stimulated by human EGF according to claim 1 wherein said monoclonal antibody is 108 produced by hybridoma cell line ATCC HB 9764.

5. A method for inhibiting the growth of human tumor cells that express EGF receptors and are mitogenically stimulated by human EGF according to claim 1 wherein said monoclonal antibody is further characterized by its capability to inhibit the growth of human oral epidermoid carcinoma (KB) cells by binding to the extra-cellular domain of the human EGF receptor of said KB cells in an antigen-antibody complex.

6. A therapeutic composition comprising an amount of monoclonal antibody and an anti-neoplastic agent effective to inhibit the growth of human tumor cells that express human EGF receptors and are mitogenically stimulated by human EGF in association with a pharmaceutical carrier; (i) wherein the antibody binds to the extracellular domain of the human EGF receptor of the tumor cells; (ii) wherein the antibody is not conjugated to the anti-neoplastic agent; and (iii) wherein the antibody inhibits the binding of EGF to the EGF receptor.

7. A therapeutic composition according to claim 6 wherein said anti-neoplastic agent is doxorubicin.

8. A therapeutic composition according to claim 6 wherein said anti-neoplastic agent is cisplatin.

9. A therapeutic composition according to claim 6 wherein said monoclonal antibody is 108 produced by hybridoma cell line ATCC HB 9764.

* * * * *

UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO. : 6,217,866, B1
DATED : April 17, 2001
INVENTOR(S) : Schlessinger et al.

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

Column 10,
Line 9, now reads "IgM(●—574)," should read -- IgM(●—●), --

Column 35,
Line 48, now reads "inhibit" should read -- inhibits --

Signed and Sealed this

Eleventh Day of December, 2001

Attest:

Nicholas P. Godici

Attesting Officer

NICHOLAS P. GODICI
Acting Director of the United States Patent and Trademark Office

E

2

#10 Terminal Disclaimer

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants : Schlessinger et al.
Serial No. : 07/244,737
Filed : September 15, 1988
For : MONOCLONAL ANTIBODY SPECIFIC TO HUMAN EPIDERMAL GROWTH FACTOR RECEPTOR AND THERAPEUTIC METHODS EMPLOYING SAME

Group Art Unit :
Examiner :

TERMINAL DISCLAIMER

Honorable Commissioner of
Patents and Trademarks
Washington, D.C. 20231

Sir:

Rorer Biotechnology Inc., assignee of the entire right, title, and interest in and to the above-identified application, by virtue of an assignment of the above identified application filed November 15, 1988, hereby disclaims the terminal 15 months of any patent which may issue on the above-identified application or on any application entitled to the benefit of the filing date of the above-identified application under 35 USC §120.

The terms of this terminal disclaimer are binding upon any grantee, its successors or assigns.

Rorer Biotechnology Inc.

By: _____
Alain Schreiber
Vice President

Dated: February 14th 1990

F

UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO. : 6,217,866, B1
DATED : April 17, 2001
INVENTOR(S) : Schlessinger et al.

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

Column 10,
Line 9, now reads "IgM(●—574)," should read -- IgM(●—●), --

Column 35,
Line 48, now reads "inhibit" should read -- inhibits --

Signed and Sealed this

Eleventh Day of December, 2001

Attest:

Nicholas P. Godici

Attesting Officer

NICHOLAS P. GODICI
Acting Director of the United States Patent and Trademark Office

PTO Logo

G

Patent Number: 6217866 **Application Number:** 08487761

	4th Year	8th Year	12th Year
Opening	04/19/2004	04/17/2008	04/17/2012
Surcharge	10/19/2004	10/20/2008	10/18/2012
Closing	04/18/2005	04/17/2009	04/17/2013

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Cetuximab Chronological Index of FDA Communications

Date	Type	Addressee	Subject	Binder #
5/10/1994	TCR	From: K. Krantz To: Dr. R. Cohen	Outcome of study; Submission of to IMCL's plans for C225 and pre-IND meeting	1
5/13/1994	TCR	From: K. Schneider To: J. Archbold	Submission of to	1
7/6/1994	TCR	From: K. Krantz To: D. Schneider	C22 -IND meeting plans; Compassionate IND close-out	1
7/22/1994	Letter	From: ImClone To: FDA	Pre-IND Meeting Document for C225 - aEGFrAb Anti-Epidermal Growth Factor Receptor Chimeric Antibody	1
8/11/1994	TCR	From: K. Krantz To: D. Green	C225 Toxicology testing	1
8/19/1994	TCR	From: F. Kaltovitch To: K. Krantz	C225 Pre-IND Review and Meeting	1
9/9/1994	TCR	From: Dr. R. Nordin To: K. Krantz, J. Gilly	C225 pre-IND Product Reviewer's Comments	1
10/14/1994	Amendment 000	Kathryn Zoon	Initial IND application (Release Protocol Lot 423704)	1
10/20/1994	Letter	Kathryn Zoon	Additional copies of Initial IND	1
10/20/1994	TCR	From: K. Schneider To: K. Krantz	C225 #5804	1
11/3/1994	Letter	From: FDA To: K. Krantz	October 26, 1994 Letter advising the assignment of an IND number for C225 (BB-IND 5804)	1
1/5/1995	Letter	From: FDA To: K. Krantz	December 30, 1994 Letter regarding comments following review of IND 5804 initial submission	1
2/6/1995	Amendment 001	Kathryn Zoon	Information Amendment - CMC (Release Protocol Lot 500301), Protocol Amendment - Change in Protocol (Version 2.0 CP02-9401) and New Investigator	1
3/10/1995	Amendment 002	Kathryn Zoon	Protocol Amendment - New Protocol (CP02-9502, CP02-9503)	1
3/23/1995	Amendment 003	Kathryn Zoon	General Correspondence - Change in regulatory contact	1
4/4/1995	TCR	From: J. Gilly To: K. Schneider	Status of submission IND #5804, Serial No. 002	1
4/10/1995	TCR	From: J. Gilly To: K. Schneider	Review of protocols CP02-9502 and CP02-9503	1
4/13/1995	TCR	From: M. Fauntleroy To: J. Gilly	Protocol CP02-9502 and CP02-9503C225, Anti-EGF receptor chimeric antibody	1
4/17/1995	Amendment 004	Kathryn Zoon	Response to FDA Request for Information - product, manufacturing, clinical; Protocol Amendment - Change in Protocol (CP02-9401, Version 3.0)	1
7/24/1995	Amendment 005	Kathryn Zoon	Information Amendment - Chemistry/Microbiology (Release Protocol Lot 950012)	1
8/3/1995	Amendment 006	Kathryn Zoon	Initial Safety Report - Mfg. Control #95/02/00005	1
8/24/1995	Amendment 007	Kathryn Zoon	Initial Safety Report - Mfg. Control #95/02/00007	1
9/5/1995	Amendment 008	Kathryn Zoon	Protocol Amendment - Change in Protocol CP02-9502, Version 3.0 - Amendments 1 &2; CP02-9503, Version 3.0	1
9/12/1995	Amendment 009	Kathryn Zoon	Protocol Amendment - Change in Protocol (CP02-9503)	1
11/20/1995	TCR	From: Dr. R. Justice To: J. Gilly	Patient #1302-UVA-CP02-9502, compassionate use	1

* TCR- Telecontact Report

Cetuximab Chronological Index of FDA Communications

Date	Type	Addressee	Subject	Binder #
11/20/1995	TCR	From: J. Gilly To: K. Schneider	Patient #1302-UVA-CP02-9502, compassionate use	1
11/21/1995	TCR	From: K. Schneider To: J. Gilly	Patient #1302-UVA-CP02-9502, compassionate use	1
11/29/1995	Amendment 010	Kathryn Zoon	Initial Safety Report - Mfg. Control #95/02/00009	1
11/30/1995	Amendment 011	Kathryn Zoon	Protocol Amendment - New Protocol (CP02-9502, Version 3.1)	1
12/8/1995	Amendment 012	Kathryn Zoon	Initial Safety Report - Mfg. Control #95/02/00011	1
12/15/1995	TCR	From: J. Archbold To: K. Schneider	Protocol changes to FDA/CBER	1
12/18/1995	Amendment 013	Kathryn Zoon	Protocol Amendment - New Protocol (CP02-9504)/Change in Protocol (CP02-9503, Amendments 4 & 5)	1
1/15/1996	Amendment 014	Kathryn Zoon	Annual Report	1
2/27/1996	Regulatory file	J. Gilly	Protocol CP02-9502 - Patient #3407	1
3/13/1996	Amendment 015	Kathryn Zoon	Protocol Amendment - New Protocol (CP02-9605)/Change in Protocol (CP02-9504, Versions 3.0 & 4.0)	1
4/18/1996	TCR	From: J. Archbold To: K. Schneider	To inquire who the reviewer for 5804 IND and what procedure to follow for teleconference to discuss comments (12/4/94 letter)	1
4/24/1996	Amendment 016	Kathryn Zoon	Request for Telephone Conference	1
5/9/1996	Amendment 017	Kathryn Zoon	General Correspondence - single patient exemption	1
5/9/1996	TCR	From: J. Gilly To: K. Schneider	Single patient exemption for C225 therapy (compassionate use)	1
5/9/1996	TCR	From: K. Schneider To: J. Gilly	Single patient exemption for C225 therapy (compassionate use)	1
5/10/1996	TCR	From: J. Gilly To: K. Schneider	Single patient exemption for C225 Therapy (Compassionate Use)	1
5/15/1996	Amendment 018	Kathryn Zoon	Protocol Amendment - New Protocol (CP02-9606)	1
5/15/1996	TCR	From: K. Schneider To: J. Gilly	Submission Serial No. 016-Re: Request for telephone conference	1
5/30/1996	Amendment 019	Kathryn Zoon	Other - Final Study Report (CP02-9401)	1
6/18/1996	Amendment 020	Kathryn Zoon	Initial Safety Report - Mfg. Control #95/02/00018	1
6/18/1996	TCR	From: Dr. J. LaBorda To: J. Gilly	IND Amendment letter: April 24, 1996; Serial No. 016 (request for phone conference)	1
6/21/1996	TCR	From: J. Gilly To: Dr. J. LaBorda, Dr. E. Bonvini	Phone conference pertaining to IND Amendment letter: April 24, 1996, Serial No. 016	1
7/1/1996	Amendment 021	Kathryn Zoon	Information Amendment - CMC (Release Protocol Lot 960159)	1
8/27/1996	Amendment 022	Kathryn Zoon	Information Amendment - CMC (Release Lot 960223); Protocol Amendment - Change in Protocol (CP02-9503, Version 7.0; CP02-9605. Version 2.0)	1
11/1/1996	Amendment 023	Kathryn Zoon	Protocol Amendment - Change in Protocol (CP02-9504, Amendment letter)/New Protocol (CP02-9607); Information Amendment - CMC (Release Lot 960275)	1
11/1/1996	TCR	From: J. Gilly To: K. Schneider	Submission Serial No. 023-Re: Clinical protocol IMCL CP02-9607	1

* TCR- Telecontact Report

Cetuximab Chronological Index of FDA Communications

Date	Type	Addressee	Subject	Binder #
12/3/1996	TCR	From: K. Schneider To: J. Gilly	Submission Serial No. 023-Re: Clinical protocol IMCL CP02-9607	1
12/17/1996	Amendment 024	Kathryn Zoon	Initial Safety Report - Mfg. Control #96/02/00023	1
1/10/1997	Amendment 025 (via Fax)	From: J. Gilly To: K. Schneider	General Correspondence - single patient protocol exemption (CP02-9504)	1
1/10/1997	TCR	From: J. Gilly To: K. Schneider	Fax submission Serial No. 025-Re: Clinical protocol IMCL CP02-9504 single patient exemption	1
1/14/1997	Fax	From: J. Archbold To: Dr. B. Parker	Fax submission Serial No. 025-Re: Clinical protocol IMCL CP02-9504 single patient exemption	1
1/14/1997	TCR	From: Dr. B. Parker To: J. Falcey	Fax submission Serial No. 025-Re: clinical protocol IMCL CP02-9504 single patient exemption (forwarded	1
1/14/1997	TCR	From: Dr. B. Parker To: J. Falcey	Fax submission Serial No. 025-Re: clinical protocol IMCL CP02-9504 single patient exemption ; has reviewed the protocol)	1
1/15/1997	Amendment 025	Kathryn Zoon	General Correspondence - Hard copy of faxed documents	1
1/15/1997	TCR	From: K. Schneider To: J. Gilly	C225 Review Team	1
1/28/1997	Amendment 026	Kathryn Zoon	Annual Report	1
3/21/1997	Amendment 027	Kathryn Zoon	Other - Final Study Report (CP02-9502)	1
4/18/1997	Amendment 028	Kathryn Zoon	Information Amendment - CMC (Release Lot 960430); Protocol Amendment - Change in Protocol (CP02-9607, Version 4.0; CP02-9608, Version 4.0)	1
5/16/1997	TCR	From: K. Schneider To: J. Gilly	NBC Report regarding ImClone products	1
5/27/1997	Amendment 029	Kathryn Zoon	Initial Safety Report - Mfg. Control #97/02/00028	1
5/30/1997	Amendment 030	Kathryn Zoon	Follow-up to a Written IND Safety Report - Mfg. Control #97/02/00028	1
6/16/1997	Amendment 031	Kathryn Zoon	Protocol Amendment - Change in Protocol (CP02-9504, Version 6.0);Other - FDA Contact Authorization	1
7/8/1997	Amendment 032	Kathryn Zoon	Protocol Amendment - New Protocol (CP02-9709, Version 1.0)	1
7/29/1997	Fax	From: G. Toolan To: K. Schneider	Information regarding BB-IND 5804. experienced by Patient 1101 in CP02-9709 (filed as Serial No. 032)	1
7/29/1997	TCR	From: J. Gilly, G. Toolan To: K. Schneider	3-day Telephone Report regarding :	1
7/30/1997	Amendment 033	Kathryn Zoon	Protocol Amendment - Change in Protocol (CP02-9608, Version 5.0; CP02-9607, Version 4.1; CP02-9605, Versions 3.0 & 4.0); Protocol Amendment - New Investigator (CP02-9605, Information Amendment - Chemistry & Microbiology (Release protocol Lot 970002)	1
8/5/1997	Amendment 034	Kathryn Zoon	Initial Safety Report - Mfg. Control #97/02/00034	1
8/25/1997	Amendment 035	Kathryn Zoon (Attn: Sharon Sickafuse)	General Correspondence - Single patient exemption protocol (CP02-9712)	1

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Date	Type	Addressee	Subject	Binder #
8/25/1997	TCR	From: J. Gilly, G. Toolan To: S. Sickafuse	Protocol CP02-9712 Compassionate use	1
8/27/1997	TCR	From: J. Gilly, G. Toolan To: S. Sickafuse	Report a grade [illegible]	1
9/2/1997	TCR	From: G. Toolan To: S. Sickafuse	Compassionate Use Protocol	1
9/2/1997	TCR	From: K. Schneider To: G. Toolan	Compassionate Use Protocol-CP02-9712	1
9/4/1997	Amendment 036	Kathryn Zoon	Initial Safety Report - Mfg. Control #97/02/00037	1
9/4/1997	TCR	From: Dr. B. Parker To: G. Toolan	Compassionate Use Protocol-CP02-9712	1
9/15/1997	Amendment 037	Kathryn Zoon	Protocol Amendment - Change in protocol (CP02-9712)	1
10/21/1997	Amendment 038	Kathryn Zoon	General Correspondence - background information re: EGFr expression as requested by clinical reviewer)	1
11/14/1997	Amendment 039	Kathryn Zoon	Protocol Amendment - New Protocol (CP02-9710, Version 3.0,); Other - Meeting Request	1
11/14/1997	Other	Kathryn Zoon	Additional Copies of Amendment 039	1
11/17/1997	TCR	From: S. Sickafuse To: G. Toolan	Serial No. 039-Teleconference request	1
11/20/1997	TCR	From: S. Dayton To: G. Toolan	Scheduling of teleconference	1
11/26/1997	TCR	From: G. Toolan To: S. Sickafuse	Report in CP02-9608	1
12/1/1997	Amendment 040	Kathryn Zoon	Protocol Amendment - Change in Protocol (CP02-9504, Version 6.0; CP02-9608, Version 6.0); Information Amendment - Chemistry & Microbiology (Release Protocol Lot 970311)	1
12/5/1997	Amendment 041	Kathryn Zoon	Initial Safety Report - Mfg. Control #97/02/00041	1
12/15/1997	Amendment 042	Kathryn Zoon	Initial Safety Report - Mfg. Control #97/02/00042	1
12/23/1997	Amendment 043	Kathryn Zoon	General Correspondence - Teleconference agenda, issues list and meeting attendees	1
12/29/1997	Amendment 044	Kathryn Zoon	Protocol Amendment - Change in Protocol (CP02-9607, Version 5.0); Protocol Amendment - New Investigator (CP02-9608. , CP02-9710,	1
1/6/1998	TCR	From: G. Toolan To: S. Sickafuse	Verify telephone number for teleconference initiated by ImClone	1
1/12/1998	Amendment 045	Kathryn Zoon	FDA Request for Information (Response to FDA's letter of 12/11/97 re: human blood-derived products)	1
1/21/1998	Amendment 046	Kathryn Zoon	General Correspondence - Meeting Minutes	1
2/2/1998	Amendment 047	Kathryn Zoon	Annual Report; General Correspondence - Meeting Request	1
2/3/1998	TCR	From: S. Sickafuse To: J. Gilly	Meeting request	1
2/5/1998	Amendment 048	Kathryn Zoon	Protocol Amendment - New Investigator (CP02-9710,	1
2/5/1998	TCR	From: S. Dayton To: J. Gilly	Conference call to review data and strategy	1

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Date	Type	Addressee	Subject	Binder #
2/25/1998	Letter	From: FDA To: J. Gilly	February 19, 198 Letter of Meeting minutes from teleconference discussing sponsor's new Phase 2 protocol (CP02-9710) which studies C225 alone in patients with (amendments 35 and 42)	1
3/2/1998	Amendment 049	Sharon Risso	General Correspondence (Pre-meeting information for virus validation teleconference)	1
3/3/1998	TCR	From: G. Toolan To: S. Sickafuse	Compassionate Use Protocols-France and Japan	1
3/5/1998	Amendment 050	Sharon Risso	General Correspondence (Request for compassionate treatment of a single patient with	1
3/6/1998	Amendment 051	Sharon Risso	Protocol Amendment - Change in Protocol (CP02-9710, Versions 4.0, 4.1, 4.2;	1
3/11/1998	TCR	From: J. Gilly, G Toolan To: S. Sickafuse	3-day safety report and compassionate treatment protocol	1
3/12/1998	Amendment 052	Sharon Risso	FDA Request for Information (Response to two questions posed by during review of compassionate treatment protocol).	1
3/12/1998	TCR	From: Dr. B. Parker To: J. Gilly, G. Toolan	Pancreatic Cancer Compassionate Protocol	1
3/13/1998	Amendment 053	Sharon Risso	Initial Safety Report - Mfg. Control #98/02/00070	1
3/13/1998	Amendment 054	Sharon Risso	FDA Request for Information (Revised IC as requested by during 3/12 telephone conversation regarding a single patient treatment protocol)	1
3/18/1998	TCR	From: J. Gilly To: S. Sickafuse	Protocol CP02-9811	1
3/20/1998	TCR	From: S. Sickafuse To: J. Gilly	Protocol CP02-9811	1
4/6/1998	Amendment 055	Sharon Risso	General Correspondence - Meeting Minutes	1
4/17/1998	Amendment 056	Sharon Risso	Protocol Amendment - New Investigator (CP02-9710,); Information Amendment - Clinical	1
4/30/1998	Amendment 057	Sharon Risso	Initial Safety Reports - Mfg Control #98/002/00071 and #98/02/00072	1
5/11/1998	Letter	From: FDA To: J. Gilly	May 5, 1998 Letter of Meeting minutes from telephone conversation held on March 25, 1998 to review ImClone's current virus validation program and to provide input as to the development of future approaches to virus validation.	1
5/18/1998	Amendment 058	Sharon Risso	Information Amendment - Chemistry (Release Protocol Lot 980077)	1
5/22/1998	Amendment 059	Sharon Risso	Initial Safety Reports - Mfg Control #98/02/00074, #98/02/00076, #98/02/00077	1
6/12/1998	Amendment 060	Sharon Risso	Information Amendment - Clinical (Addendum 1.0 to Version 4.0 of IB); Protocol Amendment - Change in Protocol (CP02-9607, Version 6.0; CP02-9709, Versions 2.0 and 2.1)	1
7/15/1998	Amendment 061	Sharon Risso	Initial Safety Report - Mfg. Control #98/02/00081	1

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Date	Type	Addressee	Subject	Binder #
7/23/1998	Amendment 062	Sharon Risso	Initial Safety Report - Mfg. Control #98/02/00083, #98/02/00084	1
8/17/1998	Amendment 063	Sharon Risso	Information Amendment - Chemistry (Release protocol Lot 980253); Protocol Amendment - New Investigator CP02-9608; A4 IRB approval for CP02-9710; revised Form FDA 1572 for CP02-9710)	1
9/9/1998	TCR	From: S. Sickafuse To: J. Gilly	IFNa and C225 Combination Protocol	1
9/9/1998	TCR	From: S. Sickafuse To: J. Gilly, G. Toolan	Regulatory Procedure for IFN Trial	1
9/18/1998	Amendment 064	Sharon Risso	FDA Request for Information (PK information); Other - Final Study Report (CP02-9503); General Correspondence - Teleconference Request	1
10/13/1998	TCR	From: G. Toolan To: S. Sickafuse	C225 Phase III Protocols-single meeting request	1
10/15/1998	TCR	From: M. Serabian To: G. Toolan	PK Submission (Serial No. 064)	1
10/16/1998	Amendment 065	Sharon Risso	Initial Safety Report – Mfg. Control #98/02/00095	1
11/2/1998	Amendment 066	Sharon Risso	General Correspondence – Request for Meeting (pre-pivotal trial mtg. C225 + radiation)	1
11/2/1998	TCR	From: Dr. D. Green To: G. Toolan	IND Serial No. 064-PK Information	1
11/3/1998	TCR	From: J. Gilly To: Dr. D. Green	Basis of C225 Dose Selection Question	1
11/4/1998	TCR	From: Dr. D. Green To: J. Gilly, G. Toolan	Review of Interim PK Report	1
11/6/1998	TCR	From: S. Dayton To: J. Gilly	C225 Pre-Phase III meeting-provide alternate dates	1
11/9/1998	Fax	From: S. Dayton To: J. Gilly	Meeting Announcement (confirming 1/7/99 meeting date and time): To receive FDA input on designee of Phase 3 trial	1
11/9/1998	TCR	From: S. Dayton To: J. Gilly	C225 Pre-Phase III meeting-Only date available is January 7, 1999 from 3-4:30pm	1
11/13/1998	Amendment 067	Sharon Risso	Protocol Amendment – Change in Protocol (CP02-9608, Ver. 7.0;	1
12/7/1998	Amendment 068	Sharon Risso	General Correspondence – Meeting Attendees	1
12/11/1998	Amendment 069	Sharon Risso	Information Amendment – Chemistry (Release Protocol Lot 980452)	1
12/21/1998	Amendment 070	Sharon Risso	General Correspondence – Responsible Head Change	1
12/24/1998	Amendment 071	Sharon Risso	General Correspondence – Meeting Attendees Revision	1
1/4/1999	Amendment 072	Sharon Risso	Annual Report	2
1/5/1999	TCR	From: G. Toolan To: S. Sickafuse	Scheduled meeting of January 7, 1999	2

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Date	Type	Addressee	Subject	Binder #
1/5/1999	TCR	From: P. Keegan, B. Parker To: H. Waksal	BB-IND 5804 -	2
1/5/1999	TCR	From: B. Parker To: J. Archbold	Call for	2
1/11/1999	TCR	From: S. Sickafuse To: G. Toolan	FDA Request for information	2
1/19/1999	Amendment 073	Sharon Risso	General Correspondence (Request for compassionate treatment of patient with	2
1/19/1999	TCR	From: G. Toolan To: S. Sickafuse	Compassionate protocol	2
1/21/1999	TCR	From: Dr. B. Parker To: G. Toolan	Patient narratives for patients with and single patient compassionate protocol	2
1/21/1999	TCR	From: S. Sickafuse To: G. Toolan	Patient narratives for patients with	2
1/22/1999	Amendment 074	Sharon Risso	General Correspondence (Minutes of Jan 7 meeting)	2
1/26/1999	TCR	From: S. Sickafuse To: G. Toolan	narratives	2
1/27/1999	TCR	From: S. Sickafuse To: G. Toolan	C225 Product Issues	2
1/29/1999	Amendment 075	Sharon Risso	FDA Request for Information (additional information regarding patients with while in a C225 study)	2
2/11/1999	Amendment 076	Sharon Risso	Protocol Amendment – Change in Protocol (CP02-9710, ver 5;), Protocol Amendment – New Investigator (Change in PI - CP02-9710), Protocol Amendment – New Protocol (CP02-9815, ver 2,), FDA Request for Information (Response to request for plan to use historical control for C225 alone in studies)	2
2/11/1999	TCR	From: G. Toolan To: S. Sickafuse	CP02-9815, version 2.0	2
2/16/1999	Letter	From: FDA To: H. Waksal	February 10, 1999 Letter of Meeting minutes - January 7, 1999 pre-Phase III meeting with ImClone regarding Chimeric Monoclonal Antibody (C225) to Epidermal Growth Factor Receptor	2
3/1/1999	TCR	From: G. Toolan To: S. Sickafuse	Protocol CP02-9815	2
3/16/1999	TCR	From: B. Shaw To: G. Toolan	Update of projected submission of BLA	2
3/17/1999	TCR	From: G. Toolan To: B. Shaw	Projected date of BLA filing (C225)	2
4/8/1999	Amendment 077	Sharon Risso	General Correspondence – Meeting Request (pre-pivotal trial meeting – ECOG study)	2
4/12/1999	TCR	From: S. Sickafuse To: G. Toolan	FDA Submission Serial No. 077-Request for meeting	2

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Date	Type	Addressee	Subject	Binder #
4/19/1999	TCR	From: G. Toolan To: S. Sickafuse	Compassionate treatment of patient	2
4/20/1999	Amendment 078	Sharon Risso	General correspondence – Compassionate treatment CP02-9921 (	2
4/21/1999	Amendment 079	Sharon Risso	General Correspondence – Compassionate treatment CP02-9920 (	2
4/21/1999	TCR	From: G. Toolan To: S. Sickafuse	Compassionate treatment-	2
4/23/1999	TCR	From: Dr. B. Parker To: G. Toolan	Compassionate treatment protocols	2
4/23/1999	TCR	From: G. Toolan To: S. Sickafuse	Compassionate treatment protocols	2
4/26/1999	TCR	From: G. Toolan To: Dr. B. Parker	Compassionate Treatment-	2
4/28/1999	TCR	From: G. Toolan To: Dr. B. Parker	Compassionate treatment-	2
4/29/1999	TCR	From: Dr. B. Parker To: G. Toolan	Compassionate Treatment patient	2
5/7/1999	Amendment 080	Sharon Risso	Protocol Amendment – New Investigator (CP02-9815;	2
5/7/1999	Amendment 081	Sharon Risso	General Correspondence – Compassionate treatment CP02-9922	2
5/7/1999	TCR	From: G. Toolan To: S. Sickafuse	Compassionate treatment patient	2
5/13/1999	TCR	From: G. Toolan To: S. Sickafuse	Compassionate treatment-	2
5/13/1999	TCR	From: S. Sickafuse To: J. Archbold	BB-IND 5804	2
5/27/1999	TCR	From: G. Toolan To: S. Sickafuse	Change in PI and site for study CP02-9922	2
6/11/1999	Amendment 082	Sharon Risso	General Correspondence (Responsible Head Designation); Information Amendment – Chemistry (Release Protocol – Lot #990002 [(Finished Goods), 990001=Final Container]); Protocol Amendment – New Investigator (CP02-9922 CP02-9815,	2
6/11/1999	TCR	From: G. Toolan To: S. Sickafuse	Introductions and electronic vs. paper BLA submissions	2
7/8/1999	TCR	From: G. Toolan To: S. Sickafuse	Single patient compassionate treatment-	2
7/12/1999	Amendment 083	Glen Jones	General Correspondence – Compassionate Treatment CP02-9924	2
7/12/1999	Amendment 084	Glen Jones	Protocol Amendment – New Investigator (CP02-9815, (	2
7/14/1999	TCR	From: S. Sickafuse To: G. Toolan	Single patient compassionate treatment-	2
8/3/1999	TCR	From: G. Toolan To: M. Fauntleroy	Electronic BLA	2
8/4/1999	E-mail	From: M. Fauntleroy To: G. Toolan	CALA questionnaire	2
8/6/1999	Amendment 085	Glen Jones	General Correspondence - Compassionate Treatment CP02-9927	2

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Date	Type	Addressee	Subject	Binder #
8/6/1999	TCR	From: K. Winestock To: G. Toolan	Compassionate Treatment	2
8/11/1999	Amendment 086	Glen Jones	Protocol Amendment – New Protocol (CP02-9816, 539); Protocol Amendment – New Investigator (CP02-9815,	2
8/11/1999	TCR	From: Dr. S. Jerian To: G. Toolan	Compassionate exemption	2
8/12/1999	TCR	From: M. Trapani To: S. Sickafuse	Plans regarding the Cetuximab BLA	2
8/16/1999	TCR	From: G. Toolan To: S. Sickafuse	Adverse Event	2
9/1/1999	Amendment 087	Glen Jones	General Correspondence – Compassionate Treatment CP02-9928	2
9/3/1999	TCR	From: Dr. S. Jerian To: M. Trapani	Compassionate treatment request-	2
9/13/1999	Amendment 088	Glen Jones	Other – Meeting Request (Pre-BLA CMC Meeting)	2
9/14/1999	TCR	From: M. Fauntleroy To: G. Toolan	Electronic BLA Guidance	2
9/14/1999	TCR	From: S. Sickafuse To: G. Toolan	Pre-BLA CMC Meeting Request	2
9/17/1999	Amendment 089	Glen Jones	Protocol Amendment – New Investigator (CP02-9709, CP02-9815, E5397, CP02-9816,	2
9/22/1999	Fax	From: S. Sickafuse To: M. Trapani	Meeting Announcement: November 4, 2001 pre-BLA CMC	2
10/1/1999	TCR	From: M. Trapani To: S. Sickafuse	Pre-BLA CMC Meeting Package	2
10/6/1999	Amendment 090	Glen Jones	Information Package – Meeting November 4, 1999 (pre-BLA CMC meeting)	2
10/7/1999	Amendment 091	Glen Jones	Protocol Amendment – New Protocol (CP02-9923,	2
10/13/1999	Amendment 092	Glen Jones	Information Amendment – Chemistry (Release protocol Lot 990261; Comparability protocols, RP0299-01, DP0299-07, DP0299-10; Research report RR0298-15; Research report RR0299-02)	2
10/15/1999	Amendment 093	Glen Jones	Protocol Amendment – New Protocol Compassionate Treatment (CP02-Compassionate,	2
10/21/1999	Amendment 094	Glen Jones	Initial Safety Report - Mfg. Control #98/02/00118	2
10/22/1999	TCR	From: S. Sickafuse To: G. Toolan	CP02-Compassionate	2
10/25/1999	TCR	From: G. Toolan To: S. Sickafuse	CP02-Compassionate	2
10/27/1999	Amendment 095	Glen Jones	General Correspondence (Compassionate treatment release of product)	2
10/27/1999	TCR	From: S. Sickafuse To: G. Toolan	CP02-Compassionate	2
10/29/1999	Amendment 096	Glen Jones	Protocol Amendment – New Protocol (CP02-9814 ver 2	2

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Date	Type	Addressee	Subject	Binder #
10/29/1999	TCR	From: S. Sickafuse To: G. Toolan	Pre-BLA CMC Meeting	2
11/1/1999	Amendment 097	Glen Jones	FDA Request for Information (Correspondence to Serial No. 093, Compassionate Treatment Protocol)	2
11/2/1999	Amendment 098	Glen Jones	General Correspondence – Meeting Questions (CMC)	2
11/2/1999	Amendment 099	Glen Jones	Compassionate Treatment – Patient Condition	2
11/5/1999	Amendment 100	Glen Jones	General Correspondence – Meeting Presentation	2
11/10/1999	Letter	From: G. Toolan To: G. Frykman	Desk copy of Version 5.0 of the Cetuximab Investigator's Brochure	2
11/11/1999	Amendment 101	Glen Jones	IND Clinical Hold – Complete Response	2
11/16/1999	TCR	From: M. Trapani To: Dr. Jerian	To discuss the clinical hold on Protocol CP02-Compassionate	2
11/19/1999	Amendment 102	Glen Jones	IND Cross-reference –	2
11/24/1999	Amendment 103	Glen Jones	General Correspondence	2
11/26/1999	Letter	From: FDA To: M. Trapani	Clinical Hold - CP02	2
11/30/1999	TCR	From: M. Trapani To: S. Sickafuse	To confirm whether FDA granted an emergency IND	2
12/1/1999	Amendment 104	Glen Jones	General Correspondence (IND Cross-reference	2
12/1/1999	Amendment 105	Glen Jones	General Correspondence (IND Cross-reference –	2
12/1/1999	Amendment 106	Glen Jones	General Correspondence (IND Cross-reference	2
12/2/1999	TCR	From: M. Trapani To: B. Friedman	User fee discussion	2
12/20/1999	Letter	From: FDA To: M. Trapani	November 4, 1999 meeting minutes - pre-BLA CMC meeting	2
12/22/1999	Amendment 107	Glen Jones	Protocol Amendment – New Investigator (CP02-9815,	2
12/27/1999	Memo	From: M. Trapani To: All	FDA Meetings Minutes-November 4, 1999 (distributed internally)	2
1/12/2000	Amendment 108	Glen Jones	General Correspondence (Cross Reference letter –	2
1/13/2000	Amendment 109	Glen Jones	General Correspondence (Cross Reference letter –	2
1/13/2000	Amendment 110	Glen Jones	General Correspondence (Cross Reference letter –	2

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1/14/2000	Amendment 111	Glen Jones	Response to FDA Request for Information (Virus clearance and validation information)	2
1/25/2000	Amendment 112	Glen Jones	Protocol Amendment – New Protocol (CP02-9813, ; Protocol Amendment – New Investigator (CP02-9815, CP02-992 CP02-9816,	2
2/1/2000	Amendment 113	Glen Jones	Other – CALA Questionnaire	2
2/2/2000	TCR	From: M. Fauntleroy To: G. Toolan	EBLA teleconference and demo	2
2/15/2000	Amendment 114	Glen Jones	Initial safety report (Mfg control # 99/02/00166)	2
2/15/2000	TCR	From: G. Toolan, D. Lynch To: S. Sickafuse	Follow up o Serial No. 111-Final Plan	2
2/15/2000	TCR	From: D. Lynch To: S. Sickafuse	IND Safety Report - Serial No. 114	2
2/18/2000	Amendment 115	Glen Jones	General Correspondence (Cross reference letter	2
2/22/2000	Amendment 116	Glen Jones	Initial safety report follow up – 7-day (Mfg control # 99/02/00166)	2
2/23/2000	TCR	From: S. Sickafuse To: D. Lynch	T Validation Program as submitted as IND Amendment Serial No. 111, 11January 2000	2
2/24/2000	Amendment 117	Glen Jones	General Correspondence (Cross reference letter –	2
2/25/2000	Amendment 118	Glen Jones	Annual Report	2
2/28/2000	Amendment 119	Glen Jones	Extra copy of annual report	2
2/29/2000	Amendment 120	Glen Jones	General Correspondence (Cross reference letter –	2
2/29/2000	Amendment 121	Glen Jones	General Correspondence (Cross reference letter –	2
3/6/2000	Amendment 122	Glen Jones	General Correspondence (Cross reference letter –	2
3/6/2000	Amendment 123	Glen Jones	Protocol Amendment – Change in Protocol (E5397, Addendum 1; CP02-9923, ver 2); Protocol Amendment – New Investigator (CP02-9814, CP02-9815, ; CP02-98 ; CP02-9923,	2
3/8/2000	Amendment 124	Glen Jones	Response to FDA Request for Information	2
3/10/2000	Amendment 125	Glen Jones	Response to FDA Request for Information (Withdrawal of CP02-Compassionate)	2
3/10/2000	TCR	From: Dr. Jerian To: M. Trapani	Follow-up discussion on the use of Protocol CP02-Compassionate	2
3/10/2000	TCR	From: S. Jerian To: M. Trapani	To determine the use of Protocol CP02-Compassionate	2
3/14/2000	TCR	From: S. Sickafuse To: G. Toolan	Compassionate protocol teleconference	2

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3/15/2000	Amendment 126	Glen Jones	Initial Safety Report (Mfg control # 00/02/00193)	2
3/15/2000	Amendment 127	Glen Jones	Information Amendment – CMC (Release Protocol, Lot 990388 [(Finished Goods), 990387=Final Container] Lot 990609; Stability Reports SR0086-01, SR0101, SR0111)	2
3/15/2000	Amendment 128	Glen Jones	General Correspondence (Cross reference letter	2
3/16/2000	Letter	From: G. Toolan for M. Trapani To: S. Sickafuse	Draft Protocol for Compassionate Treatment Teleconference - via Fax	2
3/21/2000	Amendment 129	Glen Jones	General correspondence (Cross reference letter – DAKO)	2
3/21/2000	Memo		ODAC Meeting Minutes	2
3/22/2000	Amendment 130	Glen Jones	IND Safety report – 7 day follow-up (Mfg. Control # 00/02/00193)	2
3/24/2000	Amendment 131	Glen Jones	IND Safety report –15 day (Mfg. Control #00/02/00200)	2
3/24/2000	Amendment 132	Glen Jones	Protocol Amendment – New Investigator (CP02-9815, ; CP02-9816. CP02-9923,)ther (Cross reference,	2
3/24/2000	TCR	From: S. Sickafuse To: D. Lynch	To arrange for a teleconference to discuss ImClone's Cetuximab Program	2
3/31/2000	Letter from FDA	To: M. Trapani From: Glen Jones	Withdrawal of protocol,	2
4/4/2000	Amendment 133	Glen Jones	Other - eBLA demo	2
4/7/2000	TCR	From: S. Sickafuse To: D. Lynch	To request resubmission of the ECOG Clinical Protocol (E5379) contained in the March 6, 2000 (Serial No. 123) IND Amendment and follow-up to our request for a teleconference to discuss the viral validation program	2
4/13/2000	TCR	From: S. Sickafuse To: D. Lynch	Arrange for teleconference to discuss Cetuximab program	2
4/17/2000	Letter	From: D. Lynch To: S. Sickafuse	Notification of availability of ImClone representatives to discuss the Cetuximab Viral Validation plan. - Via Fax	2
4/18/2000	TCR	From: D. Lynch To: S. Sickafuse	Arrange for teleconference to discuss Cetuximab program	2
4/19/2000	Letter	From: FDA To: Manufacturers of Biological Products	Notification to be cautious not to use materials that may be contaminated with BSE and to take measures to ensure that any materials used in production, that have been received from countries where BSE exists, do not contain BSE	2
4/21/2000	Fax	From: D. Lynch To: S. Sickafuse	Telephone conference information; date, time, phone # to call and participant code	2
4/21/2000	TCR	From: D. Lynch To: Dr. Jerian	To arrange for a teleconference regarding the Compassionate Use Program	2
4/24/2000	TCR	From: D. Lynch To: Dr. Jerian	Teleconference to discuss Compassionate Use Program and Cetuximab Development	2

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4/27/2000	Amendment 134	Glen Jones	Information Amendment – CMC (Release Protocol, Lot 990764, Lot 990819; Stability Reports SR0059-04, SR0060-04, SR0062-03, SR0072-03, SR0101-01, SR0109)	2
4/28/2000	Amendment 135	Glen Jones	General Correspondence (Cross reference letter –	2
5/1/2000	Amendment 136	Glen Jones	Protocol Amendment – Change in Protocol (E5397, Addendum 1); Protocol Amendment – New Investigator (CP02-9815, E5397, CP02-9816, CP02-9923,	2
5/4/2000	Fax	From: D. Lynch To: Dr. C. Fuchs	List of ImClone representatives who participated in the 5/4/00 teleconference regarding the Cetuximab viral validation program	2
5/4/2000	TCR	From: D. Lynch To: Drs. Fuchs and Webber	Teleconference to discuss the Cetuximab Program	2
5/5/2000	Amendment 137	Glen Jones	Response to FDA Request for Information (Copies of all current protocols & summary of all protocol amendments)	2
5/11/2000	Amendment 138	Glen Jones	Protocol Amendment – New Protocol (CP02-0035, version 1)	2
5/23/2000	TCR	From: P. Delaney To: J. Falcey	ImClone's 800 number (Call Center)	2
5/24/2000	Amendment 139	Glen Jones	Safety Report – Second Follow up (Mfg Control #99/02/00166)	2
5/24/2000	Amendment 140	Glen Jones	General Correspondence (Record of Contact – April 24, 2000 Compassionate Use Protocol)	2
5/31/2000	TCR	From: Dr. Jerian To: G. Toolan	Compassionate protocol CP02-0035	2
6/1/2000	Amendment 141	Glen Jones	Protocol Amendment – New Investigator (E5397, CP02-9816, CP02-9923,	2
6/1/2000	Amendment 142	Glen Jones	General Correspondence (Cross reference letter –	2
6/7/2000	TCR	From: G. Toolan To: S. Sickafuse	Clinical Strategy Meeting-Days of week to request	2
6/9/2000	TCR	From: Dr. Jerian To: G. Toolan	Clarification of lung cancer experience	2
6/13/2000	Amendment 143	Glen Jones	Other-Meeting Request (Clinical Strategy)	2
6/13/2000	TCR	From: D. Lynch To: Dr. J. Meisler	Investigation of shipment error of June 9, 2000 Orphan Drug Submission	2
6/13/2000	TCR	From: D. Lynch To: K. Robertson	Investigation of shipment error of June 9, 2000 Orphan Drug Submission	2

* TCR- Telecontact Report

Cetuximab Chronological Index of FDA Communications

Date	Type	Addressee	Subject	Binder #
6/14/2000	TCR	From: D. Lynch To: K. Robertson	Investigation of shipment error of June 9, 2000 Orphan Drug Submission	2
6/15/2000	Letter	From: M. Trapani To: M. Haffner	Extension to the 90 day response timeframe defined in your letter of March 20, 2000 for our Orphan-Drug Designation Request for Cetuximab (application #00-1330)	2
6/15/2000	TCR	From: D. Lynch To: Dr. J. Bona	Call was to alert the Office of Orphan Drugs that ImClone will be requesting an extension for the Response to the March 20, 2000 letter	2
6/16/2000	TCR	From: G. Toolan To: D. Ellsworth	Notification of construction of commercial facility	2
6/19/2000	TCR	From: S. Sickafuse To: G. Toolan	Clinical strategy meeting briefing book	2
6/27/2000	Fax	From: E. McFadden To: G. Toolan	Meeting Announcement: 8/11/00	2
6/27/2000	TCR	From: M. Trapani To: K. Souter	Request for FDA meeting-facility	2
6/28/2000	Amendment 144	Glen Jones	Initial 7 Day IND Safety Report (Mfg Control #00/02/00316)	2
6/28/2000	TCR	From: M. Trapani To: S. Sickafuse	Fax regarding SAE	2
6/29/2000	Amendment 145	Glen Jones	Initial 15 Day IND Safety Report (Mfg. Control #00/02/00312)	2
6/29/2000	Amendment 146	Glen Jones	Initial 15 Day IND Safety Report (Mfg. Control #00/02/00301)	2
6/29/2000	Amendment 147	Glen Jones	Initial 15 Day IND Safety Report (Mfg. Control #00/02/00302)	2
6/30/2000	Amendment 148	Glen Jones	Follow-Up to 7 Day IND Safety Report (Mfg. Control #00/02/00316)	2
6/30/2000	TCR	From: M. Trapani To: R. Abrahams	Request for FDA meeting-facility	2
7/3/2000	Letter	From: M. Haffner To: D. Lynch	Letter announcing that cetuximab qualifies for orphan designation for the treatment of	2
7/10/2000	Letter	From: M. Trapani To: D. Ellsworth	Proposal of meeting dates for the discussion of the design of the manufacturing facility	2
7/11/2000	Amendment 149	Glen Jones	Other – Meeting Package (clinical strategy meeting)	2
7/11/2000	Amendment 150	Glen Jones	Initial 7 Day IND Safety Report (Mfg. Control #00/02/00324)	2
7/11/2000	TCR	From: G. Toolan To: S. Sickafuse	Single patient exemption-CP02-0035	2
7/12/2000	TCR	From: M. Needle To: Dr. Jerian	Patient exemption for Compassionate Use	2
7/12/2000	TCR	From: S. Sickafuse To: G. Toolan	-Compassionate Use	2
7/13/2000	Amendment 151	Glen Jones	Safety Report-Follow-up (Mfg. Control Nos. 00/02/00301,00/02/00302, 00/02/00324)	2
7/13/2000	Amendment 152	Glen Jones	Single Patient Exemption Request	2

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Date	Type	Addressee	Subject	Binder #
7/13/2000	TCR	From: G. Toolan To: S. Sickafuse	Compassionate Use	2
7/14/2000	TCR	From: G. Toolan To: S. Sickafuse	Single patient exemption-CP02-0035	2
7/17/2000	Amendment 153	Glen Jones	Pre-clinical Safety Report (Mfg. Control #PC 00/02/001)	2
7/18/2000	Amendment 154	Glen Jones	Information Amendment-CMC (Release Protocol Lot No. 000007 & Stability Report SR-0073-04)	2
7/24/2000	Amendment 155	Glen Jones	Initial IND Safety Report-15 Day (Mfg. Control No. 00/02/00334)	2
7/24/2000	TCR	From: Dr. S. Jerian To: D. Lynch	message Re: IND Safety database Review	2
7/26/2000	TCR	From: Dr. S. Jerian To: D. Lynch	Clarification of FDA Request regarding the IND Safety Database Review.	2
7/27/2000	TCR	From: Dr. Serabian To: D. Lynch	Additional information for Assessment of BB-IND 5804 Serial No. 153 Review	2
7/31/2000	Amendment 156	Glen Jones	Response to FDA Request for Information (IB and immunohistochemistry reports)	2
7/31/2000	TCR	From: G. Toolan To: Dr. Serabian	Fax regarding tissue cross-reactivity reports and Investigational Brochure	2
8/2/2000	TCR	From: CA Cartier To: P. Chao	Clarification of export of clinical material.	2
8/3/2000	Amendment 157	Glen Jones	Other: Meeting Attendees	2
8/3/2000	Amendment 158	Glen Jones	Pre-clinical Safety Report Follow-up (Mfg. Control #PC 00/02/0001)	2
8/3/2000	Amendment 159	Glen Jones	Response to FDA Request for Information (Information requested by 7/27/00)	2
8/4/2000	Amendment 160	Glen Jones	Response to FDA Request for Information (Bleeding events requested by	2
8/4/2000	TCR	From: G. Toolan To: Dr. M. Serabian	Follow-up of July-telephone call	2
8/4/2000	TCR	From: G. Toolan To: S. Sickafuse	Call to S. re: information requested to be placed on desk (sent via fax); verified 8/11 meeting place and request for 5-10 additional set-up minutes	2
8/7/2000	Amendment 161	Glen Jones	IND Safety Report (Mfg. Control #00/02/00349)	2
8/7/2000	TCR	From: M. Trapani To: S. Sickafuse	FDA Contact-August 11 meeting	2
8/8/2000	Memo	From: CA. Cartier To: Reg., Sales, Marketing, Corp. Comm., H. Waksal		2
8/9/2000	TCR	From: D. Lynch To: Dr. M. Lessing	Call was to alert the Office of Orphan Drugs that ImClone will be requesting an additional extension for the Response to the March 20, 2000 letter	2
8/11/2000	Memo	From: D. Lynch To: Reg. File	ImClone's record of the August 11, 2000 meeting with the FDA	2
8/14/2000	Amendment 162	Glen Jones	IND Safety Report follow-up (Mfg. 00/02/00349)	2
8/14/2000	TCR	From: Drs. Serabian/Jerian To: G. Toolan	Follow-up information on the	2
8/18/2000	Amendment 163	Glen Jones	Information Amendment-CMC (Facility Renovations)	2

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Date	Type	Addressee	Subject	Binder #
8/18/2000	TCR	From: D. Lynch, G. Toolan To: Dr. S. Jerian	Clarification of request for safety data	2
8/21/2000	TCR	From: D. Lynch To: Dr. S. Jerian	Confirm conference call for August 25, 2000 at 9:00am to discuss Independent Review Charter.	2
8/21/2000	TCR	From: Dr. Serabian To: G. Toolan	Conversation with FDA-Monkey studies	2
8/22/2000	Amendment 164	Glen Jones	Protocol Amendment-New Protocol (CP02-9816C ver 1.0); Change in Protocol (CP02-9709, ver 3.0; CP02-9813, ver 2.0; CP02-9814, ver 3.0; CP02-0035, ver 1.1; CP02-9816, ver 4.0); New Investigator (E5397, CP02-9816, CP02-0035, Other – Authorized contact	2
8/25/2000	TCR	From: JF, DL, MN, GT To: SJ, GM	August 25, 2000 teleconference meeting minutes	2
8/29/2000	TCR	From: CA Cartier To: W. Purvis	To inquire about the CBER process for requesting acceptance of proposed proprietary names.	2
8/31/2000	TCR	From: CA Cartier To: Dr. K. Webber	To inquire about the CBER process for brand name selection.	2
8/31/2000	TCR	From: D. Lynch, J. Tarnowski To: Dr. C. Fuchs	To request clarification on "raw data" to be included in validation and characterization reports submitted to the IND and BLA.	2
9/5/2000	Amendment 165	Glen Jones	IND Safety Report (Mfg. Control # 00/02/00385)	2
9/7/2000	Amendment 166	Glen Jones	General Correspondence-Meeting Minutes (August 11, 2000 Clinical Discussion)	2
9/7/2000	Amendment 167	Glen Jones	Request for evaluation & acceptance of proposed proprietary names	2
9/7/2000	Letter	From: M. Trapani To: W. Purvis	Request for evaluation & acceptance of proposed proprietary names - DESK COPY	2
9/8/2000	Amendment 168	Glen Jones	Information Amendment - CMC (Release Protocol Lot 00C00453)	2
9/11/2000	Amendment 169	Glen Jones	General Correspondence-Minutes (August 25, 2000 Teleconference)	2
9/14/2000	Amendment 170	Glen Jones	IND Safety Report-Initial (Mfg Control #PC00/02/002; 00/02/00389)	2
9/19/2000	Amendment 171	Glen Jones	IND Safety Report 7-Day Follow-up (Mfg. Control No. 00/02/00316 (2))	2
9/21/2000	TCR	From: CA. Cartier To: D. Ellsworth, T. Emler	To inquire about available dates for a meeting to discuss the new manufacturing facility.	2
9/28/2000	Letter	From: S. Sickafuse To: M. Trapani	September 22, 2000 Letter of Meeting minutes from August 11, 2000 meeting	2
9/28/2000	TCR	From: S. Sickafuse To: D. Lynch	To inquire as to the number of electronic copies FDA requires for submission	2
9/29/2000	Amendment 172	Glen Jones	Clinical Information – Safety (Narratives Gr. 3&4 allergic reactions, bleeding events, deaths)	2
10/6/2000	Amendment 173	Glen Jones	IND Safety Report Follow-up (Mfg Control #PC00/02/002 (2))	2
10/13/2000	TCR	From: D. Lynch To: M. Fauntleroy	To discuss the formatting requirements for the electronic version of Serial No. 172	2

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Date	Type	Addressee	Subject	Binder #
10/17/2000	TCR	From: CA Cartier To: W. Purvis	To inquire about the status of Cetuximab proposed brand name review.	2
10/20/2000	TCR	From: CA Cartier To: C. Fuchs	To request clarification on Release Protocol data submitted at Serial No. 168	2
10/27/2000	Amendment 174	Glen Jones	Protocol Amendment - New Investigator (CP02-9815, CP02-9816, CP02-9816C, E539, CP02-0035,	2
11/2/2000	Amendment 175	Glen Jones	Clinical Information – Safety (Resubmission of narratives	2
11/2/2000	Amendment 176	Glen Jones	Clinical Information-HACA Assay (SOP CSOP0014, Protocol CP0013, Report CR0013)	2
11/6/2000	Amendment 177	Glen Jones	IND Safety Report-Initial (Mfg Control #00/02/00457)	2
11/13/2000	TCR	From: M. Trapani To: B. Goldman	To inquire whether references were necessary for Fast Track Designation request	2
11/14/2000	Amendment 178	Glen Jones	Request for Fast Track Designation	2
11/14/2000	Amendment 185	Glen Jones	IND Safety Report Follow-up (Mfg Control #00/02/00457)	2
11/15/2000	Amendment 179	Glen Jones	Information Amendment – Chemistry (Molecular characterization of DNA Sequencing)	2
11/15/2000	Amendment 180	Glen Jones	Information Amendment – Chemistry (Purification process description, new process testing, viral validation report and protocol)	2
11/15/2000	Amendment 181	Glen Jones	Information Amendment – Chemistry (Cell culture process and testing)	2
11/15/2000	Amendment 182	Glen Jones	Information Amendment – Chemistry (Viral Validation)	2
11/15/2000	Amendment 183	Glen Jones	Information Amendment – Chemistr	2
11/16/2000	Amendment 186	Glen Jones	General Correspondence-Change in Regulatory Contact	2
11/17/2000	Amendment 184	Glen Jones	Pre-BLA CMC Mtg. Request	2
11/17/2000	Amendment 187	Glen Jones	IND Safety Report Follow-up (Mfg. Control #PC 00/02/002 (2))	2
11/20/2000	TCR	From: D. Lynch, N. Mehta To: C. Fuchs	To provide w/update on (1) moving forward with BLA; (2) demonstrating comparability of drug substance produced at and (3) IND Amendments No. 179 to 184	2
11/21/2000	Amendment 188	Glen Jones	Information Amendment – Chemistry (Confirmation of successful outcome of clinical study CP02-9923)	2
11/22/2000	Fax	From: N. Mehta To: S. Sickafuse	BB IND 5804 for Cetuximab and our submissions 184 and 188 requesting a pre-BLA meeting.	2
11/22/2000	Fax Alert	From: D. Lynch To: S. Sickafuse	Animal Death (#PC00/02/003)	2
11/29/2000	TCR	From: CA Cartier To: W. Purvis	To inquire about the rationale for the APLS review results and recommendation of Cetuximab proposed brand names	2
11/30/2000	Amendment 189	Glen Jones	IND Safety Report-(Mfg. Control #PC00/02/0030(1))	2

* TCR- Telecontact Report

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Date	Type	Addressee	Subject	Binder #
12/4/2000	Amendment 190	Glen Jones	IND Safety Report-15 Day Report-(Mfg. Control #00/02/00454)	2
12/5/2000	Fax	From: S. Sickafuse To: N. Mehta	Pre-BLA meeting announcement-1/18/01	2
12/7/2000	Memo	From: N. Mehta To: DB, RC, MB, AD, EH, MB, GN, JT, HW, DL	Pre-BLA Meeting announcement-1/18/01	
12/11/2000	Fax Alert	From: D. Lynch To: S. Sickafuse	Animal Death (#PC00/02/004)	2
12/12/2000	Amendment 191	Glen Jones	General Correspondence (Cross reference -	2
12/13/2000	Amendment 192	Glen Jones	Annual Report	2
12/15/2000	Amendment 193	Glen Jones	Information Amendment – Chemistry (Amended Background document for CMC meeting)	2
12/15/2000	Amendment 194	Glen Jones	Protocol Amendment - New Protocol (CP02-9932, ver 1.0,	2
12/18/2000	Amendment 195	Glen Jones	IND Safety Report (Mfg. Control #PC00/02/0004)	2
12/18/2000	TCR	From: D. Lynch To: Dr. S. Jerian	Discuss ImClone's plan to study Cetuximab in the treatment IMC CP02-9932	2
12/20/2000	Amendment 196	Glen Jones	Protocol Amendment - New Protocol (CP02-0036, ver 1.0; CP02-9925, ver 1.0)	2
12/20/2000	TCR	From: D. Lynch To: S. Sickafuse	To arrange for a teleconference to discuss Cetuximab program.	2
12/21/2000	TCR	From: D. Lynch To: Dr. C. Fuchs	To arrange for a teleconference to discuss the Cetuximab comparability program for the material product at	2
12/22/2000	TCR	From: S. Sickafuse To: D. Lynch	To request ImClone provide 2 additional copies of Serial No. 193.	2
12/26/2000	Fax Alert	From: D. Lynch To: S. Sickafuse	Animal Death (#PC00/02/005)	2
1/3/2001	TCR	From: M. Serabian To: C. Cartier	To ask questions and discuss comments on the December 13, 2000 Annual Report/IB (Submission Serial No. 192).	3
1/4/2001	Amendment 197	Glen Jones	IND Safety Report (Mfg. Control #PC00/02/005)	3
1/8/2001	TCR	From: Dr. S. Jerian To: D. Lynch	Arrange for a discussion of ImClone's three proposed lung protocols (CP02-9923, CP02-9925, CP02-0036) on January 10, 2001	3
1/8/2001	TCR*	From: S. Sickafuse To: L. Lee	Dates and time for the requested Erbitux FDA meeting	1- BLA
1/8/2001	TCR*	From: S. Sickafuse To: N. Mehta	Regarding our request for a meeting to discuss the issues raised in the December 28 Letter	1- BLA
1/9/2001	Fax	To: K. Webber From: N. Mehta	ImClone participants at teleconference	3
1/10/2001	TCR	From: D. Lynch To: Dr. S. Jerian	To discuss FDA comments on ImClone's three proposed lung protocols (CP02-9923, CP02-9925, CP02-0036)	3
1/11/2001	Amendment 198	Glen Jones	General Correspondence (Cross reference letter –	3
1/11/2001	Letter from FDA	M. Trapani Frd'd to N. Mehta	January 3, 2001 Letter regarding Orphan Drug Application #00-1330	3

* TCR- Telecontact Report

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Date	Type	Addressee	Subject	Binder #
1/11/2001	TCR	From: G. Toolan To: S. Sickafuse	Clinical pre-BLA meeting and brand names review.	3
1/12/2001	Fax	From: D. Lynch To: C. Fuchs	Draft Minutes of the January 9, 2001 teleconference regarding drug substance comparability	3
1/12/2001	TCR	From: D. Lynch To: Dr. C. Fuchs	To inform . of ImClone's plans to provide for FDA review draft meeting minutes of the January 9, 2001 teleconference regarding drug substance comparability.	3
1/16/2001	Amendment 199	Glen Jones	Information Amendment-Clinical (pre-BLA meeting request)	3
1/17/2001	Amendment 200	Glen Jones	IND Safety Report (Mfg. Control #01/02/00522)	3
1/18/2001	Letter from FDA	Nikhil Mehta	January 12, 2001 Letter regarding Fast Track Designation	3
1/19/2001	Letter from FDA	Nikhil Mehta	Re: Questions 1-6; further information needed to meet criteria for Fast-track designation	3
1/22/2001	Amendment 201	Glen Jones	Protocol Amendment-New Investigator (CP02-9815, E5397, , CP02-9816, CP02-9816C, CP02-9814, Other – Authorized Contact	3
1/22/2001	Fax	From: N. Mehta To: S. Sickafuse	Request for telecon to clarify and discuss items listed in the letter dated 1/19/01.	3
1/23/2001	Amendment 202	Glen Jones	Information Amendment-Toxicology (Amendment 2 to 39-week monkey study)	3
1/24/2001	Fax	From: G. Toolan To: M. Serabian	Faxed Dose calculations used for the toxicity protocol 070-087	3
1/24/2001	TCR	From: G. Toolan, N. Mehta To: M. Serabian	Dose conversion calculations-Human to primate	3
1/25/2001	Fax	From: G. Toolan To: S. Sickafuse	Question proposed by the clinical reviewer	3
1/25/2001	E-Mail	From: M. Serabian To: G. Toolan	Dose Extrapolation	3
1/25/2001	Fax	From: N. Mehta To: S. Sickafuse	January 26, 2001 teleconference dial-in information and ImClone representatives	3
1/26/2001	TCR	To: E. McFadden From: D. Lynch	Scheduling of the pre-BLA Clinical/Pre-clinical meeting for Cetuximab BLA	3
1/30/2001	Amendment 203	Glen Jones	IND Safety Report (Mfg. Control #PC00/02/005(1))	3
1/30/2001	Fax	From: E. McFadden To: N. Mehta	Meeting Announcement-pre-BLA Clinical/Pre-clinical	3
1/31/2001	Amendment 204	Glen Jones	Protocol Amendment- New Protocol (CP02-0037, ver1.0; CP02-0038, ver 1.0; CP02-0141, ver 1.0)	3
1/31/2001	TCR	From: D. Lynch To: S. Jerian	Discuss ImClone's approach to submission of the IND Safety Report Follow-up [PC00/02/005(1)] (CLE 0070-087).	3

* TCR- Telecontact Report

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Date	Type	Addressee	Subject	Binder #
2/1/2001	Amendment 205	Glen Jones	General Correspondence-Meeting Minutes (1/9/01 telecon and meeting minutes from1/18/01 Pre-BLA CMC meeting)	3
2/2/2001	Amendment 206	Glen Jones	Information Amendment-CMC (Authorization)	3
2/2/2001	Amendment 207	Glen Jones	Response to FDA Request for Information	3
2/2/2001	TCR	From: CA. Cartier To: S. Sickafuse	To inquire about the review status of brand names for Cetuximab	3
2/6/2001	Amendment 208	Glen Jones	Response to FDA Request for Information (Response to Question 1-Letter from FDA 1/19/01)	3
2/6/2001	Amendment 209	Glen Jones	General Correspondence (1/26/01 Meeting Minutes from 1/10/01 telecon to discuss clinical issues)	3
2/6/2001	Amendment 210	Glen Jones	Response to FDA Request for Information (ASCO abstract)	3
2/6/2001	Letter	From: N. Mehta To: Internal Affairs Staff (HFY-50)	Export Authorization Request	3
2/7/2001	Amendment 211	Glen Jones	Response to FDA Request for Information (SAP, independent response committee charter and CRFs)	3
2/7/2001	TCR	From: D. Lynch To: S. Sickafuse	clarify the procedures to obtain FDA/ImClone meeting minutes	3
2/9/2001	Fax	From: D. Lynch To: C. Fuchs	Proposed table for the presentation of the information requested by CBER for the key Cetuximab lots used in the in vivo preclinical evaluations and clinical studies.	3
2/9/2001	TCR	From: D. Lynch To: Dr. C. Fuchs	cetuximab lots used in in vivo preclinical evaluations and clinical studies. of the other disciplines (clinical and to ensure the content and format of the table meet the needs of the review team.	3
2/9/2001	TCR	From: S. Jerian To: D. Lynch	To inquire if the Compassionate Use Protocol was open for enrollment	3
2/12/2001	TCR	From: D. Lynch To: S. Jerian	To discuss the Compassionate Use Protocol	3
2/15/2001	TCR	From: C. Fuchs To: D. Lynch	proposed presentation of the information requested by CBER reviewers (CMC, clinical, pharm/tox) for the key Cetuximab lots used in the in vivo preclinical evaluations and clinical studies.	3
2/20/2001	FDA letter	From: FDA To: N. Mehta	1/18/01 meeting minutes	3
2/20/2001	TCR	From: M. Fauntleroy To: CA. Cartier	To notify FDA regarding submission of the e-BLA Demo (Version 2.0) and to inquire if extra desk copies are needed.	3
2/21/2001	Amendment 212	Glen Jones	Other - eBLA Demo 2.0	3

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Date	Type	Addressee	Subject	Binder #
2/22/2001	Amendment 213	Glen Jones	Information Amendment – Clinical (Pre-BLA Clinical background document)	3
2/23/2001	Amendment 214	Glen Jones	Information amendment-Pharmacology/Toxicology (Cross reactivity study GRA00406)	3
2/23/2001	Fax	From: N. Mehta To: S. Sickafuse	Informing FDA we are sending 3 additional copies of the Background document	3
2/26/2001	Amendment 215	Glen Jones	IND Safety Report (Mfg. Control #01/02/00555Tumor Necrosis-EMR study)	3
2/28/2001	Amendment 216	Glen Jones	Information Amendment- Chemistry (Release Protocol Lot 00A00661, Lot 00C00660 [(Finished Goods), 00C00659=Final Container], Lot 00C00963 [(Finished Goods), 00C00962=Final Container]	3
3/5/2001	E-Mail	From: M. Serabian To: N. Mehta	Potential Teleconference Times	3
3/6/2001	Amendment 217	Glen Jones	Response to FDA Request for Information-Pharmacology/Toxicology (Interim report of 39-week study)	3
3/6/2001	Fax	From: G. Toolan To: M. Serabian	Interim summary report for the ImClone/Merck KGaA 39 week monkey study	3
3/7/2001	TCR	From: G. Toolan To: K. Cressotti	Export Authorization Request	3
3/7/2001	TCR	From: G. Toolan To: S. Sickafuse	Export Authorization Request	3
3/8/2001	TCR	From: G. Toolan To: K. Cressotti	Export Authorization Request	3
3/9/2001	Amendment 218	Glen Jones	Response to Request for Information (Pre-clinical lot data)	3
3/9/2001	Amendment 219	Glen Jones	Response to FDA Request for Information (Response to irinotecan in patients who progress on irinotecan)	3
3/9/2001	Amendment 220	Glen Jones	Information Amendment –Pharmacology/Toxicology (Serology report ARFC0294-11)	3
3/12/2001	Amendment 221	Glen Jones	Protocol Amendment - Change in Protocol (CP02-9816 version 5.0; CP02-0038, ver 2.0); New Investigator (CP02-9815, E5397, CP02-9816, P02-9816C, CP02-0038,	3
3/12/2001	Fax	From: G. Toolan To: M. Limoli	The names and addresses of the consignees (Export Authorization request)	3
3/16/2001	Amendment 222	Glen Jones	Response to FDA Request for Information (Percent of patients receiving C225 by process designation; table of pts. By clinical study, drug sub., Drug prod. and Ref. Mat.)	3
3/19/2001	Amendment 223	Glen Jones	Response to FDA Request for Information (EGFr positivity - Q4 and Q5 for letter dated 1/19/01)	3
3/20/2001	Amendment 224	Glen Jones	Information Amendment – Chemistry updated specification, CoA Lot 6259 and 00C00819)	3
3/21/2001	Fax	From: N. Mehta To: S. Jerian	Body of submission serial no. 223	3

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Date	Type	Addressee	Subject	Binder #
3/22/2001	Amendment 225	Glen Jones	IND Safety Report (Mfg Control #01/02/00555(1))	3
3/25/2001	Fax	From: N. Mehta To: Dr. C. Fuchs	A copy of submission no. 223 (EGFr test kit; filed 5/19/01)	3
3/26/2001	Amendment 226	Glen Jones	Response to FDA Request for Information (additional in vivo results in a refractory tumor setting – xenograft models)	3
3/26/2001	Fax	From D. Lynch To: N. Mehta	Fax forwarded at Twinbrook Conference regarding agenda for March 27, 2001 meeting	3
3/26/2001	Fax	From: D. Lynch To: S. Jerian	Copy of IND Amendment - Serial No. 226	3
3/30/2001	TCR	From: D. Lynch To: S. Jerian	To request patient with Cetuximab under a physician sponsored single patient IND.	3
3/30/2001	TCR	From: G. Toolan To: C. Fuchs	Export Authorization Request	3
4/3/2001	Amendment 227	Glen Jones	Protocol Amendment – Change in Protocol (CP02-9925, ver 2.0; CP02-9932, ver 2.0; CP02-0036, ver 2.0); Protocol Amendment – New Investigator (CP02-9815, E5397, CP02-9925, CP02-0036, CP02-0038, CP02-0141,	3
4/4/2001	Amendment 228	Glen Jones	Information Amendment – CMC (CoAs for Lonza drug product Lot 00C01177=Final Container, 01C01178=Finished Goods; corrected CoA for drug substance Lot 00A01125)	3
4/5/2001	Amendment 229	Glen Jones	General Correspondence – Meeting Minutes (March 27, 2001 pre-BLA meeting minutes)	3
4/10/2001	TCR	From: N. Mehta To: B. Goldman	To discuss plans for Rolling BLA	3
4/10/2001	TCR	From: N. Mehta To: Dr. K. Stein	To inquire about completion of review of the report	3
4/11/2001	Amendment 230	Glen Jones	Response to FDA Request for Information (et al. manuscript)	3
4/13/2001	Amendment 231	Glen Jones	General Correspondence – Meeting Minutes (April 4, 2001 teleconference); Other – Draft "Dear Doctor" Letter	3
4/16/2001	TCR	From: Dr. C. Fuchs To: N. Mehta	Comment on report	3
4/17/2001	Amendment 232	Glen Jones	General Correspondence – Meeting Minutes (eBLA teleconference)	3
4/17/2001	Fax	From: N. Mehta To: B. Friedman	Request for waiver of User Fees	3
4/20/2001	E-Mail	From: CA Cartier To: M. Fauntleroy	Attached please find the minutes from the April 6, 2001 ImClone/FDA teleconference, per your request	3
4/23/2001	Amendment 233	Glen Jones	Request for submission of portions of BLA	3
4/23/2001	TCR	From: Dr. S. Jerian To: N. Mehta	BLA and Dear Dr. letter	3
4/27/2001	Letter	From: S. Sickafuse To: N. Mehta	Meeting Minutes from 3/27/2001 - pre-BLA clinical meeting	3

* TCR- Telecontact Report

Cetuximab Chronological Index of FDA Communications

Date	Type	Addressee	Subject	Binder #
5/1/2001	Amendment 234	Glen Jones	Protocol Amendment-New Investigator: CP02-9815 - CP02-9816C - CP02-0035 - CP02-0141 - CP02-0036 -	3
5/1/2001	Amendment 235	Glen Jones	IND Safety Report-New onset, seizure/convulsion; Mfg. Control No. 01/02/00625	3
5/2/2001	Amendment 236	Glen Jones	General Correspondence: Change in Regulatory Contact	3
5/2/2001	Amendment 237	Glen Jones	Regarding electronic submission of medical imaging data	3
5/3/2001	Amendment 238	Glen Jones	Other: Follow up to telephone conversation of 4/23/01	3
5/3/2001	Amendment 239	Glen Jones	Never submitted discussed in teleconference on 5/21/2001	3
5/8/2001	Fax	From: CA Cartier To: S. Giuliani	List of ImClone representatives who participated in the 5/8/2001 teleconference regarding the Cetuximab rolling BLA submission	3
5/8/2001	TCR	From: L. Lee To: Drs. Jerian, Fuchs, Goldman, Serabian	To gain agreement on the proposed BLA timeline submitted to the FDA on 4/23/01	3
5/9/2001	Amendment 240	Glen Jones	Information Amendment-pharm/tox study 221-014	3
5/10/2001	Amendment 241	Glen Jones	Information Amendment-CMC (release of Lots 01C00095, 01C00006 [(Finished Goods); 01C00005=Final Container], 00C00963 [(Finished Goods), 00C00962=Final Container]	3
5/10/2001	Memo	From: L. Lee To: G. Mills, M. Fauntleroy	Minutes of discussion on Imaging Submission	3
5/10/2001	Memo	From: L. Lee To: M. Fauntleroy	Electronic BLA	3
5/17/2001	Amendment 242	Glen Jones	Other: revised proposal for the electronic submission of imaging data	3
5/17/2001	TCR	From: D. Lynch To: S. Giuliani	To discuss ImClone's proposal to submit Section 6 of the Cetuximab BLA along with Section 8	3
5/17/2001	TCR	From: L. Lee To: C. Fuchs	1-to discuss the amendment for the comparability report; 2-to discuss potential scenarios for the timing of the submission for the facilities	3
5/17/2001	TCR	From: L. Lee To: C. Fuchs	To follow up with the protocol amendment regarding	3

* TCR- Telecontact Report

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Date	Type	Addressee	Subject	Binder #
5/18/2001	TCR	From: C. Fuchs To: L. Lee	Guidance on timing of facilities submission	3
5/21/2001	TCR	From: D. Lynch To: D. Green, S. Giuliani	To discuss with FDA ImClone's proposal to submit Section 6 and Section 8 of the BLA	3
5/22/2001	Amendment 243	Glen Jones	Other: revised timelines for the submission of the cetuximab rolling BLA under Fast Track drug development	3
5/23/2001	TCR	From: G. Toolan, L. Lee, M. Needle To: S. Jerian	To discuss the preclinical Dear Dr. letter and dose reductions	3
5/30/2001	Fax	From: L. Lee To: S. Jerian	Attached is the revised Dear Dr. letter discussing the preclinical toxicology study and the	3
6/1/2001	TCR	From: D. Lynch To: C. Vincent	To obtain User Fee ID number for Cetuximab BLA	3
6/6/2001	Memo	FDA/ImClone	Re: Meeting with CBER's Electronic Submissions and Information Technology Groups for Demonstration of eBLA Demo 4.0	3
6/7/2001	TCR	From: D. Lynch, G. Toolan To: M. Serabian	To discuss the submission schedule and amendment contents for Section 5 (Pharmacology/Toxicology) of Cetuximab BLA	3
6/11/2001	Fax	From: N. Mehta To: C. Fuchs	CMC Table of Contents for the Cetuximab BLA	3
6/11/2001	Fax	From: G. Toolan To: M. Serabian	Draft Item 5 Table of Contents	3
6/12/2001	Amendment 244	Glen Jones	FDA Request for Information – CFRs for CP02-0141, CP02-0038, CP02-0037	3
6/12/2001	Amendment 245	Glen Jones	Other: Amended timelines for the submission of the cetuximab rolling BLA under Fast Track drug development	3
6/12/2001	Fax	From S. Sickafuse To: L. Lee	Letter regarding Rolling BLA	3
6/12/2001	Letter	From: G. Jones To: L. Lee	Rolling BLA	3
6/12/2001	TCR	From: G. Toolan To: M. Serabian	BLA Item 5: Nonclinical pharmacology and toxicology section	3
6/12/2001	TCR	From: S. Jerian To: L. Lee	Discussion of Trade Names and Coverage of C225 in lay press	3
6/14/2001	Amendment 246	Glen Jones	Amendment to the Request for Evaluation and Acceptance of proprietary names	3
6/14/2001	Fax	From: L. Lee To: S. Jerian	Revised "Dear Dr." letter to expand the discussion in the human experience and the findings in the low and mid-dose groups.	3
6/14/2001	Fax	From: L. Lee To: S. Sickafuse, S. Jerian	Fax copy of Amendment to the Request for Evaluation and Acceptance of proprietary names	3
6/15/2001	Amendment 247	Glen Jones	EBLA demo 4.0	3
6/15/2001	Fax	From: B. Friedman To: N. Mehta	Letter regarding BLA application fee waiver granted	3
6/15/2001	Letter	From: J. Axelrad To: N. Mehta	BLA application fee waiver granted	3

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Date	Type	Addressee	Subject	Binder #
6/20/2001	Amendment 248	Glen Jones	7-day IND Safety Report follow-up [Mfg. Control no. 00/02/00451 (1)]	3
6/20/2001	TCR	From: D. Lynch To: C. Vincent	To confirm the procedures for submission of the User Fee Cover Sheet	3
6/21/2001	TCR	From: D. Lynch To: F. Paul	To inquire as to the hours of operation, location of CBERs DCC and any restrictions relative to delivery of electronic submissions and paper submissions	3
6/21/2001	TCR	From: G. Toolan To: M. Serabian	BLA Item 5: Nonclinical pharmacology and toxicology section	3
6/25/2001	Fax	From: L. Lee To: S. Jerian	Summary of Safety data from pilot study (0038); proposal for inclusion of narratives and CRF's in the BLA	3
6/25/2001	TCR	From: S. Jerian To: L. Lee	Approval of "Dear Doctor" letter, trade name discussion and others	3
6/26/2001	Amendment 249	Glen Jones	Other: Dear Doctor letter (Animal deaths and skin toxicity)	3
6/26/2001	Fax	From: L. Lee To: S. Jerian	SAE for patient #1001 with :	3
6/27/2001	Letter	From: C. Limoli, Int'l. Relations To: N. Mehta	Export Authorization letter - Poland	3
6/27/2001	TCR	From: G. Toolan To: V. Carter	Export Authorization Request-Poland	3
6/27/2001	TCR	From: L. Lee To: Dr. S. Jerian	(1) Review safety data from 038 and discussion of control arm for Phase III study; (2) Inclusion of narratives and CRFs for BLA	3
6/28/2001	BLA Initiation	To: G. Jones From: LL	Initiating the Rolling BLA for cetuximab for refractory colorectal cancer	1- BLA
7/3/2001	Fax	From: N. Mehta To: C. Fuchs	The planned manufacturing schedule for Cetuximab at :	3
7/3/2001	TCR	From: L. Lee To: S. Jerian	Clarification of pre-clinical studies information and discussion of Phase 3 design	3
7/6/2001	Fax	From: L. Lee To: C. Broadnax	Summary results from the 10/10 Trademark Evaluation study conducted for IMC-C225.	3
7/9/2001	TCR	From: L. Lee To: S. Sickafuse	Rolling BLA Timeline and mechanism of submission	3
7/10/2001	TCR	From: N. Mehta To: C. Fuchs	Follow-up to BLA filing	3
7/11/2001	Amendment 250	Glen Jones	General Correspondence :	3
7/13/2001	Amendment 251	Glen Jones	Other – Proposal for SAS datasets	3
7/16/2001	TCR	From: C. Fuchs To: N. Mehta	Follow-up to BLA filing	3
7/16/2001	TCR	From: L. Lee To: Brad Glasscock	Rolling BLA timeline and mechanism of submission-Final	3
7/16/2001	TCR	From: L. Lee To: S. Jerian	Change of Medical Reviewer for C225	3
7/18/2001	Letter	From: NM To: G. Jones	Extra desk copies of two section of our rolling BLA for cetuximab; CMC section and Pharm/tox section	1- BLA

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Date	Type	Addressee	Subject	Binder #
7/19/2001	Amendment 252	Glen Jones	Protocol Amendment: Change in Protocol: CP02-9815 ver. 4.0, CP02-9925 ver. 3.0, CP02-9932 ver. 3.0, CP02-0036 ver. 3.0, Protocol Amendment: New Investigator: CP02-9815 - E5397 - CP02-0035 - CP02-0141 -	3
7/23/2001	Amendment 253	Glen Jones	Other: General Correspondence: Fax with planned manufacturing schedule for cetuximab	3
7/24/2001	Amendment 254	Glen Jones	Other: Meeting Request-CMC	3
7/24/2001	TCR	From: G. Toolan To: S. Sickafuse	Request for additional copies-IND Serial No. 252	3
7/27/2001	Amendment 255	Glen Jones	Other Information on Follow-up for Pat 1001, Study 0038	3
7/27/2001	Letter	From: L. Lee To: G. Jones	Additional copies of IND amendment 252 as requested by :	3
7/30/2001	TCR	From: L. Lee To: S. Sickafuse	Discussion on the Completion of BLA filing	3
7/31/2001	TCR	From: L. Lee To: L. Pai Scherf	Discussion of the Clinical Section of the BLA	3
7/31/2001	TCR	From: N. Mehta To: C. Fuchs	CMC amendments	3
8/6/2001	TCR	From: N. Mehta To: G. Mills	SAS data for imaging submission	3
8/8/2001	Fax	From: E. McFadden To: N. Mehta	Meeting Announcement: September 6, 2001=Pre-Supplement re: new facility & comparability w/irinotecan	3
8/9/2001	Fax	From: A. Choquette To: S. Sickafuse	Teleconference dial-in information	3
8/10/2001	Fax	From: L. Lee To: L. Pai Scherf	Clinical Section (Item 8) of the BLA	3
8/10/2001	TCR	From: L. Lee To: SS, SJ, GM, LPS, VG	Teleconference to discuss outstanding housekeeping issues fro the clinical area during the transition of Medical Reviewers, and to discuss the proposed Reviewers data base	3
8/13/2001	Amendment 256	Glen Jones	Withdrawal of Protocol #CP02-0037	3
8/13/2001	Letter	From: CBER To: LL	Assigned submission tracking number (stn) BL 125033/0	1- BLA
8/13/2001	Letter	From: G. Jones To: L. Lee	Submission Tracking Number assigned to rolling BLA.	3
8/14/2001	Amendment 257	Glen Jones	IND Safety Report Follow-up Mfg. Control #00/02/00334 (1)	3
8/14/2001	Fax	From: A. Choquette To: S. Sickafuse	List of participants from ImClone Systems Incorporated and P-Net at the teleconference 8/10/01.	3

* TCR- Telecontact Report

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Date	Type	Addressee	Subject	Binder #
8/20/2001	Fax	From: N. Mehta To: S. Sickafuse	A paper copy of CMC section of our Rolling BLA for cetuximab (STN 125033/0) is being Fed Ex'd per request.	3
8/20/2001	Fax	To: S. Sickafuse From: NM	Paper copy of CMC section being Fed Ex'd	1- BLA
8/23/2001	Amendment 258	Glen Jones	Background document for pre-SBLA mtg	3
8/23/2001	Amendment 259	Glen Jones	IND Safety Report Mfg # 01/02/00757-	3
8/23/2001	TCR	From: N. Mehta To: C. Fuchs	Discussion of PAI timelines	3
8/28/2001	TCR	From: D. Lynch To: M. D. Green	To update on the organization of the PK information in the BLA.	3
8/31/2001	TCR	From: D. Lynch To: M. D. Green	To propose that the detailed PK Summary in the BLA be incorporated in Section 6 rather that Section 8.	3
9/5/2001	Amendment 260	Glen Jones	Information Amendment – Pharm/Tox (070-087 final study report and BLA Section 5 Toxicology Summary)	3
9/5/2001	Amendment 262	Glen Jones	Information Amendment – Chemistry	3
9/5/2001	TCR	From: D. Lynch To: C. Fuchs	To request assistance in locating information regarding the	3
9/7/2001	Amendment 261	Glen Jones	Information Amendment – Clinical (Safety overview for 1st 12 patients in CP02-0038)	3
9/7/2001	TCR	From: G. Toolan To: M. Serabian	BLA Item 5: Nonclinical pharmacology and toxicology section	3
9/7/2001	TCR	From: N. Mehta To: C. Fuchs	Discussion of Specifications and response to question	3
9/10/2001	Fax	From: N. Mehta To: C. Fuchs		3
9/10/2001	Fax	To: C. Fuchs From: NM		1- BLA
9/13/2001	Amendment 263	Glen Jones	Information Amendment – Clinical (BLA discussion item agreements – FDA Reviewer's Data Base and "clock start" submission)	3
9/13/2001	Fax	From: L. Lee To: L. Pai Scherf	Information amendment submitted to IND 5804 on September 7, 2001 regarding the first twelve patients treated in the Cetuximab pilot safety study (Protocol CP02-0038).	3
9/14/2001	Fax	From: L. Lee To: L. Pai Scherf	Updated safety summary for the first 12 patients in the pilot safety study with the toxicity grade information incorporated.	3
9/18/2001	TCR	From: L. Pai Scherf To: L. Lee	An informal meeting to help orient to the BLA	3
9/20/2001	Amendment 264	Glen Jones	Information Amendment - Chemistry (Certificate of Analysis of Cetuximab Reference Standard, Lot No. 01C00314)	3
9/20/2001	Fax	From: L. Lee To: L. Pai Scherf	Information from IND Submission 223 regarding the	3

* TCR- Telecontact Report

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Date	Type	Addressee	Subject	Binder #
9/24/2001	TCR	From: *D. Lynch To: Marlene (Document Control)	To inquire if BB-IND 5804 Serial No. 264 submission (CMC-Information Amendment providing for the Certificate of Analysis of Cetuximab Reference Standard, Lot No. 01C00314) had been logged into CBERs Document Control	3
9/24/2001	TCR	From: D. Lynch To: S. Sickafuse	To inquire if BB-IND 5804 Serial No. 264 submission (CMC-Information Amendment providing for the Certificate of Analysis of Cetuximab Reference Standard, Lot No. 01C00314) had been forwarded to DARP by CBER Document Control	3
9/28/2001	Amendment 265	Glen Jones	Other: Request for Waiver for Pediatric study requirements	3
10/5/2001	Amendment 266	Glen Jones	Protocol Amendment: New Investigator: CP02-9815 - CP02-9816 - E5397 - CP02-9925 - CP02-0038 -	3
10/5/2001	Letter	From: S. Sickafuse To: Attendees	September 6, 2001, preSupplement meeting with ImClone regarding Cetuximab; IND 5804	3
10/5/2001	Letter (2nd Submission)	From: L. Lee To: G. Jones	Rolling Submission for BLA	1- BLA
10/9/2001	Fax	From: N. Mehta To: C. Fuchs	Additional details for comp. Eval. For C225 manu. At BBG, information on :	3
10/9/2001	TCR	From: N. Mehta To: C. Fuchs	BLA timing, CBERs inspection schedule, bioburden specs for cetuximab bulk, testing for product stability.	3
10/10/2001	Amendment 267	Glen Jones	Other: Discussion of Phase III Randomized Trial in First Line Metastatic Colorectal Cancer	3
10/10/2001	Fax	From: L. Lee To: L. Pai Scherf	Submission 267 (19 pages) sent Fed Ex	3
10/10/2001	Fax	From: N. Mehta To: C. Fuchs	Manufacturing schedule for upcoming runs at SP Pharmaceuticals	3
10/10/2001	Letter	From: L. Lee To: G. Jones	Hard copies of Clinical Reports for Medical Reviewers	1- BLA
10/10/2001	Letter	From: N. Mehta To: G. Jones	Reviewer Aids: CD ROMs of Reviewer Data Base	1- BLA
10/10/2001	TCR	From: L. Lee To: LPS, SS, JS, KS, CF	Follow-up on the status of Brand Name	3
10/11/2001	TCR	From: D. Lynch To: B. Hood	To confirm the receipt of the 2001 Orphan Drug Annual Report	3
10/11/2001	TCR	From: LPS, SJ, GM To: L. Lee	Post-Marketing Study Requirement	3

* TCR- Telecontact Report

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Date	Type	Addressee	Subject	Binder #
10/12/2001	TCR	From: C. Fuchs To: N. Mehta	Bioburden: agreement throughout CBER for further specs at . Comparability changes.	3
10/15/2001	Letter	From: L. Lee To: G. Jones	Post-marketing study commitment; Rolling BLA timeline	1- BLA
10/18/2001 - 12/3/2001	TCR	From: LL To: FDA	BLA Review: Running list 10/18-12/3/2001	3
10/19/2001	Fax	From: A. Choquette To: S. Sickafuse	Teleconference information for Phase III protocol on 10/30/01 at 9:45am.	3
10/19/2001	Letter	From: N. Mehta To: G. Jones	A CD as a review aid for the PK reviewer which contains the entire Item 6 and relevant portions of Item 8	1- BLA
10/19/2001	TCR	From: N. Mehta To: S. Sickafuse	Contacted at 11:30am to discuss three items.	3
10/22/2001	Fax	From: A. Choquette To: S. Sickafuse	PK reviewer aid CD-Rom tracking information.	3
10/24/2001	Letter	From: FDA To: L. Lee	Letter granting the name Erbitux as the tradename for cetuximab	3
10/25/2001	Amendment 268	Glen Jones	IND Safety Report Mfg. Control #01/02/00880-Ileus	3
10/25/2001	Fax	From: D. Lynch To: S. Sickafuse	FDA notification of an IND Safety Report for a patient being treated under the ECOG protocol describing an event, Ileus.	3
10/25/2001	Fax	From: N. Mehta To: S. Sickafuse	Attachment: letter sent to the FDA regarding the Rolling BLA timeline and Post-marketing study commitments.	3
10/25/2001	Fax	From: S. Sickafuse To: L. Lee	Brand name letter announcing acceptance of the name "Erbitux"	3
10/25/2001	Fax	From: S. Sickafuse To: L. Lee	Letter regarding post-marketing study, and receipt of a revised proposal for a post-marketing confirmatory study	3
10/25/2001	Fax	From: S. Sickafuse To: LL	Letter from FDA regarding post-marketing study	1- BLA
10/25/2001	Letter	From: CBER To: L. Lee	Comments from the review of September 7 - safety report of the first 12 patients from a pilot study January 31 - submission of protocol CP02-0037 as post-marketing confirmatory study not acceptable; August 13 - acknowledge withdrawal of protocol CP02-0037	1- BLA
10/25/2001	Letter	From: FDA To: L. Lee	Letter regarding post-marketing study, and receipt of a revised proposal for a post-marketing confirmatory study	3
10/26/2001	Letter	From: LL To: FDA - Information Management Team	Completion of Cetuximab BLA	1- BLA
10/30/2001	Amendment 269	Glen Jones	Revised Proposal for Phase III Post-Marketing Study	3
10/30/2001	Fax	From: NM To: C. Broadnax	Copy of planned press release announcing completion of the BLA filing for C225	1- BLA
10/30/2001	FDA Form	From: FDA To: L. Lee	Form FDA 2656 - stamped and initialed received 10/30/2001	1- BLA

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Date	Type	Addressee	Subject	Binder #
10/30/2001	Letter	From: L. Lee To: G. Jones	Revised proposal for Post-marketing study (CP02-0037 version 2.0)	1- BLA
10/31/2001	TCR	From: S. Sickafuse To: N. Mehta	Notification of BLA completion	3
11/1/2001	Letter	From: FDA To: L. Lee	A request from the National Cancer Institute,	3
11/2/2001	Amendment 270	Glen Jones	Request to clarify meeting minutes for the pre-supplement meeting – September 6, 2001	3
11/2/2001	Fax	From: C Broadnax To: N. Mehta	In reference to ImClone's Oct. 30, 2001 request for advisory review of the Erbitux (Cetuximab) press release that announces the filing of a Biologics License Application for Erbitux.	3
11/2/2001	Fax	From: CBER To: NM	Press release announcing the filing of a Biologics License Application for ERBITUX	1- BLA
11/5/2001	BLA Amend 001	G. Jones	Additional CMC and Clinical information and a copy of a letter detailing the Rolling BLA timelines and Planned Amendments	1- BLA
11/7/2001	Letter	From: CBER To: LL	Letter granting pediatric waiver	1- BLA
11/7/2001	Letter	From: FDA To: L. Lee	In reference to our biologics license application for Cetuximab submitted under Section 351 of the Public Health Service Act – Reference made to our correspondence dated Oct. 5, 2001, requesting a waiver of pediatric studies under 21 CFR 601.27 (c).	3
11/8/2001	TCR	From: C. Broadnax To: N. Mehta	Press release announcing the completion of the BLA filing	3
11/8/2001	TCR*	To: C. Broadnax From: N. Mehta	Press release announcing the completion of the BLA filing	1- BLA
11/9/2001	TCR	From: N Mehta 11/09/01 To: M Fauntleroy, B. Glassock, D Offringa 11/16/01To: M Fauntleroy	eBLA for Cetuximab In reference to changes in sections of the eBLA and in reference to ImClone filing an amendment by Nov. 30, 2001.	3
11/13/2001	Amendment 271	Glen Jones	IND Safety Report – 15-Day Report Mfg. Control #01/02/00902	3
11/15/2001	Amendment 272	Glen Jones	General Correspondence – Meeting Minutes - October 30, 2001 teleconference recorded by IMCL	3
11/19/2001	Fax	From: L. Lee To: L Pai Scherf	BLA #125033/0 – request for clarification on Study 9923.	3
11/20/2001	TCR	From: L. Lee To: G. Mills	IRAC's rationale for Final Overall Best Response, and Patient Population	3
11/21/2001	Amendment 273	Glen Jones	IND Safety Report – 15 Day Report Mfg. Control #01/02/00909	3
11/21/2001	Fax	From: AMC for NM To: S. Sickafuse	In reference to IND Safety report: Being sent via mail, and by fax in case of a delay due to the upcoming holiday.	3

* TCR- Telecontact Report

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Date	Type	Addressee	Subject	Binder #
11/21/2001	Fax	From: L. Lee To: L Pai Scherf	BLA #125033/0 – request for clarification on Study 9923.	
11/21/2001	Fax	From: N Mehta To: R Neal, C Fuchs	Information which was requested regarding the preparation of the :	3
11/29/2001	BLA Amend 002	G. Jones	Modified versions of Items 11, 12 and the Statistical folder.	1- BLA
11/29/2001	Fax	From: L. Lee To: L Pai Scherf	List (chart) of patients who died within 30 days of the last dose of Cetuximab.	3
12/3/2001	BLA Amend 003	G. Jones	CP02-0141 study update, fax to : (11/19/01) ; (11/26/01) CP02-9923 :	1- BLA
12/3/2001	E-mail	From: L. Lee To: G. Mills	Memo regarding Clarification of Variables and Programs.doc	3
12/4/2001	TCR	From: L. Lee To: LPS, GM	Follow-up review issues - comparator scans and IRAC assessments	3
12/4/2001	Fax	From: L. Lee To: L. Pai Scherf, G. Mills	Clarification of data issues	3
12/4/2001	TCR*	To: G. Mills, L. Pai-Scherf From: LL	Follow-up on Review Issues-Comparator Scans and IRAC Assessment	1- BLA
12/5/2001	TCR	From: L. Lee To: G. Mills, L. Pai-Scherf	Request for consolidation of list of issues resolved and clarification of comparator scans	3
12/5/2001	TCR*	To: G. Mills, L. Pai-Scherf From: LL	Request for Consolidation of List of Issues Resolved, and Clarification of Comparator Scans	1- BLA
12/7/2001	BLA Amend 004	G. Jones	Updates all TOCs and index files in the BLA and BLA Amends	1- BLA
12/12/2001	TCR	From: G. Mills, L. Pai-Scherf To: L. Lee	Communication of issues and expectations from ImClone on BLA	3
12/12/2001	TCR*	From: L. Lee To: G. Mills, L. Pai-Scherf	Communication on Issues and Expectations from ImClone on BLA	1- BLA
12/14/2001	TCR	From: L. Lee, C. Anderson To: G. Mills		3
12/14/2001	TCR*	To: G. Mills From: LL		1- BLA
12/17/2001	Amendment 274	Glen Jones	Protocol Amendment – Change in Protocol (CP02-9932, Ver. 4.0); New Investigator (CP02-9815, CP02-9932,	3

* TCR- Telecontact Report

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Date	Type	Addressee	Subject	Binder #
12/18/2001	BLA Amend 005	G. Jones	BLA Amend Materials to comply with several requests from FDA Medical Review Team	1- BLA
12/26/2001	BLA Amend 006	J. Siegel	Request for Meeting and Deferral of Filing Decision Version 1 and Version 2 - Via fax	1- BLA
12/26/2001	Fax	From: L. Lee To: JS, KZ, KS, GJ, PK, GM, LPS, SS (ver 1); KZ, KS, GJ, SS, KW, PK, RS, GM, LPS	Request for Meeting and Deferral of Filing Decision	1- BLA
12/26/2001	TCR*	From: L. Lee To: K. Stein	Inform FDA of the Letter Requesting a Deferral of Filing Decision & Request for Meeting	1- BLA
12/28/2001	Fax	From: S. Sickafuse To: L. Lee	RTF letter	1- BLA
12/28/2001	Fax	From: N. Mehta To: S. Sickafuse/ C. Broadnax	ImClone Press Release CBER communication	1- BLA
1/3/2002	TCR*	To: G. Mills From: LL	Informing FDA of Cancer Letter publication	1- BLA
1/4/2002	TCR*	From: L. Lee To: P. Keegan	Discussion with on .	1- BLA
1/7/2002	Amendment 275	Jay Siegel	Request for Meeting to Discuss Issues in December 28, 2001 Refusal-to-File Letter from the FDA	4
1/7/2002	Fax	From: L. Lee To: S. Sickafuse	Agenda for proposed meeting with FDA to discuss the 12/28/2001 RTF letter from FDA	4
1/8/2002	Memo	From: L. Lee To: Regulatory File	Computer printout provided on IRAC assessment	4
1/9/2002	Letter	From: FDA To: L. Lee	December 28, 2001 Letter regarding Refusal to File	1- BLA
1/9/2002	TCR*	From: N. Mehta To: S. Sickafuse	Schedule meeting for February 19 so will be present	1- BLA
1/10/2002	TCR	From: D. Lynch To: S. Sickafuse	To inquire if the Preclinical and Clinical Study Reports being included in the IND Annual Report are required to contain the Data Listing	4
1/16/2002	TCR*	From: L. Lee To: S. Sickafuse	Schedule Formal Meeting	1- BLA
1/17/2002	Amendment 276	From: L. Lee To: J. Siegel	Request for Meeting to Discuss Issues in December 28, 2001 Refusal-to-File Letter from the FDA	4
1/17/2002	Fax	From: L. Lee To: S. Sickafuse	Request for Meeting	
1/17/2002	Fax	From: L. Lee To: S. Sickafuse	Request for Meeting - Filed to IND Amendment 276	4
1/18/2002	TCR*	From: L. Lee To: P. Keegan, K. Stein	Inform FDA of Congressional Inquiry	1- BLA
1/22/2002	Fax	From: E. McFadden To: L. Lee	Meeting Announcement: confirmation - 2/26/02 10:00am - 12:00pm, WOC1, Rm 1	4
1/31/2002	Amendment 277	G. Jones	IND Safety Report - Initial 02/02/00977; 15 Day Follow up 00/02/00389 (1)	4
1/31/2002	Fax	From: D. Lynch To: S. Sickafuse	IND Safety Report Alert - (Serial No. 277)	4

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Date	Type	Addressee	Subject	Binder #
1/31/2002	TCR	From: N. Mehta To: C. Fuchs	Timing of :	4
2/1/2002	Amendment 278	G. Jones	Annual Report	4
2/4/2002	Amendment 279	G. Jones	Protocol Amendment - New Investigator: CP02-9815 CP02-9932	4
2/6/2002	Amendment 280	G. Jones	General Correspondence - Submission of faxes sent to FDA 12/26/2001	4
2/6/2002	Amendment 281	G. Jones	CMC Amendment - Three Lot Analyses Data (Lot No.'s 01C00010, 01C00090 [(Finished Goods); 01C00089=Final Container] 01C00503)	4
2/8/2002	Amendment 282	G. Jones	February 26, 2002 Meeting Briefing Packet	4
2/12/2002	Amendment 283	G. Jones	Protocol Amendment - New Investigator: CP02-9815	4
2/12/2002	Fax	From: L. Lee To: R. Yetter	Return of Fed Ex box inadvertently sent to the Document Control Room	4
2/12/2002	Fax	From: L. Lee To: R. Yetter	Return of Fed Ex box inadvertently sent to the Document Control Room - fax with letter	4
2/13/2002	Amendment 284	G. Jones	Initial 15-day IND Safety Report-Inguinal Abcsess (mfg. 02/02/00936); Initial 15-day IND Safety Report- (mfg. 02/02/00996)	4
2/13/2002	Fax	From: L. Lee To: S. Sickafuse	Faxed copy of Amendment 284 - IND Safety Reports (Mfg. 02/02/00936; Mfg. 02/02/00996)	4
2/14/2002	Fax	From: L. Lee To: C. Saffron	IND Amendments	4
2/14/2002	TCR	From: L. Lee To: LP Scherf	Inform of IND Amendments	4
2/15/2002	Amendment 285	G. Jones	7 Day Notification and Initial 15-day IND Safety Report (mfg. 01/02/00946)	4
2/15/2002	Fax	From: L. Lee To: S. Sickafuse	Faxed copy of Amendment 285 - IND Safety Report (Mfg. 01/02/00946)	4
2/15/2002	Fax	From: L. Lee To: C. Saffron	Draft - of IND Amendment	4
2/19/2002	Letter	From: L. Sperry To: J. Little, CBER	Lonza 483 Response	4
2/20/2002	Amendment 286	G. Jones	General Correspondence - Revised questions for the Feb. 26th 2002 Meeting	4
2/21/2002	287	G. Jones	Protocol Amendment - EMR 62 202-007, EMR 62 202-009, EMR 62 202-010	4
2/21/2002	288	G. Jones	IND Safety Report - 01/02/00593	4
2/21/2002	Fax	From: L. Lee To: S. Sickafuse	Requested information by and	4
2/25/2002	Fax	From: L. Lee To: S. Sickafuse	Documents in preparation for 2/26/2002 meeting	4
2/25/2002	Fax	From: L. Lee To: S. Sickafuse	Attachments in preparation for 2/26 meeting	4
2/25/2002	Fax	From: L. Lee To: L.Scherf	get copy from send from Washington, DC	4
2/27/2002	Amendment 289	G. Jones	Protocol for EMR 62 202-009	4
2/27/2002	Amendment 290	G. Jones	Additional pre-meeting information for 2/26/02	4

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Date	Type	Addressee	Subject	Binder #
2/28/2002	Fax	To: R. Cooper From: L. Lee	TCR to regarding: Inform of IND Amendments	4
3/1/2002	Fax	From: CBER To: L. Lee	Regarding protocol	4
3/1/2002	Letter	FDA/ImClone	Teleconference to discuss plans for Independent Review Committee	4
3/5/2002	Amendment 291	G. Jones	IND Safety Report Follow-up -01/02/00946(1)	4
3/8/2002	Amendment 292	G. Jones	General correspondence - Cross Reference Letter for :	4
3/8/2002	Amendment 293	G. Jones	IND Safety Report Follow-up [02/02/00977 (1)]	4
3/18/2002	Amendment 294	G. Jones	IND Safety Report Follow-up (02/02/01045)	4
3/18/2002	Amendment 295	G. Jones	Meeting Minutes: February 26, 2002	4
3/19/2002	Letter (Amendment 295)	G. Jones	Additional copies of IND Amendment 295	4
3/22/2002	Amendment 296	G. Jones	IND Safety Report - 15 day initial 02/02/01040 -	4
3/22/2002	Amendment 297	G. Jones	Protocol Amendment: Change in Protocol (CP02-0038, CP02-0141, E5397) Protocol Amendment: New Investigator (CP02-9815 - ; CP02-9816 - ; CP02-9816C - CP02-9923 - CP02-9608 - CP02-9502 -	4
3/25/2002	TCR	From: N. Mehta To: S. Sickafuse	Clinical Meeting for 4/15/2002	4
4/5/2002	Amendment 298	G. Jones	Request for Clinical Guidance Meeting and Pre-Meeting Package	4
4/8/2002	Amendment 299	G. Jones	IND Safety Report - 15-day Follow-Up Report Mfg. Control # 02/02/01045 (1)	4
4/18/2002	Facsimile	From: S. Sickafuse To: L. Lee	Meeting Announcement: confirmation - 6/4/2002	4
4/23/2002	TCR	From: N. Mehta To: C. Fuchs	Discuss BB36 amendment and 007 supply	4
4/25/2002	Facsimile	From: S. Sickafuse To: L. Lee	Reschedule to 5/28/2002; teleconference originally scheduled for 6/13/2002	4
4/25/2002	TCR	From: L. Scherf To: L. Lee	Inquiry about ImClone's position on the requirement of the Test Dose	4
5/2/2002	Amendment 300	G. Jones	BB36 Comparability	4
5/2/2002	Amendment 301	G. Jones	Initial 15-Day IND Safety Report - (Mfg. 02/02/01093)	4
5/3/2002	TCR	From: L. Lee To: L. Pai-Scherf	Determine FDA Teleconference and Meeting dates; heads up on protocols to be submitted	4
5/6/2002	Amendment 302	G. Jones	Protocol Amendment: New Protocol (CP02-0144)	4
5/6/2002	Amendment 303	G. Jones	Protocol Amendment: New Protocol (CA225005 [BMS])	4
5/9/2002	Amendment 304	G. Jones	IND Safety Report - 15-day Follow-Up Report Mfg. Control # 02/02/01093 (1) -	4
5/9/2002	Letter	From: FDA To: L. Lee	Letter informing us of the Clinical Trials Data Bank available at http://clinicaltrials.gov.	4

* TCR- Telecontact Report

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Date	Type	Addressee	Subject	Binder #
5/9/2002	Letter (Amendment 302)	G. Jones	Additional copies of IND Amendment 302	4
5/9/2002	TCR	From: LL, NM To: PK, LPS, GM	Increase of Sample Size for 007	4
5/13/2002	Letter (Amendment 303)	G. Jones	Additional copies of IND Amendment 303	4
5/23/2002	Fax	To: S. Sickafuse From: L. Lee	Preparation for the May 28th telecon and June 4 meeting in DC	4
5/24/2002	Fax	To: S. Sickafuse From: L. Lee	Dial-in information for 5/28/2002 teleconference to discuss 1) re-analysis plan for 9923 & 0141, 2) IRC for 007, 9923 & 0141, 3) Study EMR 62 202-007, 4) proposal for AE analysis in the BLA resubmission	4
5/30/2002	Amendment 305	G. Jones	IND Safety Report - 15 Day initial 02/02/01075 -	4
5/30/2002	Amendment 306	G. Jones	Cetuximab IB Version 8.0 - dated May 28, 2002	4
5/30/2002	Fax	To: S. Sickafuse From: D. Lynch	IND Safety Report - 15 Day initial 02/02/01075 -	4
5/30/2002	Fax	To: S. Sickafuse From: L. Lee	Preparation for June 4th FDA meeting	4
6/3/2002	Fax	To: L. Lee From: S. Sickafuse	Agenda for tomorrows meeting (6/4/2002)	4
6/3/2002	Letter (Amendment 306)	G. Jones	3 additional copies of Amendment 306	4
6/3/2002	TCR	From: AM Choquette To: D. Slavin	Request for additional copies of Submission Serial No. 303	4
6/7/2002	Amendment 307	G. Jones	May 28, 2002 Teleconference minutes and Presentation from from 6/4/2002 FDA meeting	4
6/7/2002	Fax	From: L. Lee To: S. Sickafuse	Attendees at the May 28th Teleconference	4
6/10/2002	TCR	From: N. Mehta To: C. Fuchs	Status of IND Amendment for BB36	4
6/11/2002	Amendment 308	G. Jones	15-Day IND Safety Report - Erythema Nodosum - mfg. Control no. 02/02/01120	4
6/19/2002	Amendment 309	G. Jones	Release Protocol for Lot 01C00098	4
6/20/2002	Amendment 310	G. Jones	General Correspondence (SWOG - S0205); Cross reference letter for	4
6/20/2002	Amendment 311	G. Jones	Protocol Amendment: New Investigator CA225005)	4
6/21/2002	E-Mail	From: L. Lee To: BMS, Merck, IMCL	May 28th teleconference meeting minutes as recorded by ImClone	4
6/28/2002	Amendment 312	G. Jones	Meeting request for Clinical Dev. Plan and Pre-meeting package	4
6/28/2002	TCR	To: D. Lynch From: G. Mills, S. Jerian	FDA called to request ImClone provide the Monitoring Plans for all on-going active clinical trials across all INDs	4

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Date	Type	Addressee	Subject	Binder #
6/28/2002 Amended 7/1/2002	TCR	To: D. Lynch From: G. Mills, S. Jerian	FDA called to request ImClone provide the Monitoring Plans for all on-going active clinical trials across all INDs	4
7/1/2002	TCR	From: N. Mehta To: C. Fuchs	Discuss the status of IND amendment 300 (BB36)	4
7/2/2002	Amendment 313	G. Jones	Response to FDA Request for Information -	4
7/2/2002	Fax	From: N. Mehta To: D. Slavin / S. Sickafuse	Request for Meeting for Clinical Development Plan	4
7/3/2002	Amendment 314	G. Jones	Request for Meeting for Clinical Development Plan	4
7/3/2002	Amendment 315	D. Slavin	Request for Meeting for Clinical Development Plan	4
7/3/2002	Fax	From: N. Mehta To: D. Slavin / S. Sickafuse	Request for Meeting for Clinical Development Plan	4
7/3/2002	Letter	From: S. Sickafuse To: N. Mehta	FDA's Meeting Minutes from 5/28/02 Teleconference	4
7/9/2002	Fax	From: N. Mehta To: C. Fuchs	A comparison of Bioburden Test Methods for Cetuximab Drug Substance	4
7/10/2002	Amendment 316	G. Jones	Response to FDA Request for Information - Monitoring Plans - 007, 005 (BMS), 0141, 0038, 9925, 0036, E5397, 9923, 0144, 9932	4
7/10/2002	Letter	From: S. Sickafuse To: L. Lee	Memo of June 4, 2002 meeting	4
7/12/2002	Fax	From: S. Sickafuse To: L. Lee	Meeting scheduled on 9/17 @ 1pm at the FDA	4
7/15/2002	Amendment 317	G. Jones	General Correspondence: TCR re: use of BB 36 C225 material in clinical studies	4
7/15/2002	TCR	From: C. Fuchs To: N. Mehta	Discuss the status of IND amendment 300 (BB36)	
7/17/2002	Amendment 318	G. Jones	IND Safety Report: 15-dav Initial Report (Mfg. Control #02/02/01192);	4
7/24/2002	Amendment 319	G. Jones	Protocol Amendment: New Investigator - CP02-0144 - CA225005 - CP02-9815 -	4
7/26/2002	Amendment 320	G. Jones	Initial IND Safety Report - possible pancreatitis (Mfg. Control #02/02/01193)	4
7/29/2002	Letter	From: S. Sickafuse To: L. Lee	FDA sent letter concerning clinical issues at	4
7/29/2002	TCR	Dr. Lee Pai Scherf & Dr. George Mills	Clarifications on Investigation	4
8/2/2002	Fax	From: L. Lee To: G. Jones	7-day Notification initial (Mfg. Control #02/02/01200)	4
8/5/2002	Amendment 321	G. Jones	Information Amendment - CMC - Revised Drug Product Specification to reflect the introduction of a new method for the detection of endotoxin	4
8/6/2002	TCR	Dr. Lee Pai Scherf & Dr. George Mills	Clarifications on Investigation	4
8/8/2002	Amendment 322	G. Jones	Protocol Amendment: New Investigator (CP02-0144, : Additional Information CP02-0144, CP02-9815, CA225005,	4

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Date	Type	Addressee	Subject	Binder #
8/9/2002	Amendment 323	G. Jones	15-day Safety Report - 7 Dav Notification (Mfg. Control #02/02/01200) =	4
8/9/2002	Fax	From: L. Lee To: Lee Pai Scherf, George Mills	Mtg. Minutes faxed from 7/26/02 and 8/6/02	4
8/14/2002	Amendment 324	G. Jones	CoA for BB36: Drug Product Lot #02C0001B; CoA for Drug Substance Lot # 01J01563	4
8/15/2002	Amendment 325	G. Jones	Other: Revised and Final IRC Charter and Associated Documents	4
8/16/2002	TCR	From: L. Lee To: G. Mills	Revised and Final IRC Charter	4
8/19/2002	TCR	From: L. Lee To: P. Delaney, T. Poigo	Updates on progress of Expanded Access Program	4
8/20/2002	E-Mail	From: L. Lee To: George Mills	Zip files of the Final IRC Charter and Associated Documents (includes CD Rom of files)	4
8/26/2002	Amendment 326	G. Jones	IND Safety Reports: 15-day Follow-up [Mfg. Control #02/02/01193 (1)]; 15-day Follow-up [Mfg. Control #02/02/01200 (1)]	4
8/30/2002	Amendment 327	G. Jones	Amendment to Pre-Meeting Package for September 17, 2002 meeting with FDA	4
8/30/2002	Fax	From: L. Pai Scherf To: George Mills	Prepared Copy of BB-IND 5804 Serial #327	4
9/4/2002	Amendment 328	G. Jones	Protocol Amendment: New Investigator (CP02-0144;	4
9/5/2002	Amendment 329	G. Jones	IND Safety Report-15-Day Initial Report - (Mfg. Control #11996212, 11999893, 1206564)	4
9/9/2002	Amendment 330	G. Jones	IND Safety Report - 15-Day Follow-up [Mfg. Control #02/02/01193 (2)] Confirmation of final diagnosis:	4
9/17/2002	Facsimile	From: D. Lynch To: S. Sickafuse, L. Scherf	7-Day Notification: Mfg. Control #02/02/01250)	4
9/17/2002	Memo		September 17, 2002 Meeting Attendance List	4
9/17/2002	Memo		September 17, 2002 Meeting Presentation* (ImClone) *An electronic copy can be obtained in X:Group/410/Submissions/BB IND 5804-C225/BB IND 5804 Serial No. 327	4
9/20/2002	Amendment 331	G. Jones	IMCL CP02-0144 CRF	4
9/20/2002	TCR	From: L. Lee To: L. Pai-Scherf	Request for information from FDA on Study CP02-0144	4
9/23/2002	TCR	From: C. Fuchs To: N. Mehta	SAE investigation and PTR lot usage	4
9/24/2002	Amendment 332	G. Jones	New Protocol = CA225004 (Medical Monitor; CA225004, Monitoring Plan vAugust 16, 2002	4
9/24/2002	Fax	From: L. Lee To: L. Pai-Scherf	Discussion on IRC Charter: Dial-in information	4

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Date	Type	Addressee	Subject	Binder #
9/25/2002	Amendment 333	G. Jones	IND Safety Report - 15-Day Initial (Mfg. Control #02/02/01250)	4
9/25/2002	TCR	From: G. Mills, L. Pai-Scherf To: L. Lee	FDA comments on the IRC Charter	4
9/27/2002	Fax	From: L. Lee To: G. Mills, L. Pai-Scherf	List of attendees from the 9/25/02 teleconference pertaining to the IRC Charter	4
10/1/2002	Fax	From: L. Lee To: G. Mills, L. Pai-Scherf	Expanded Access Program (EAP) Outline	4
10/1/2002	Fax	From: L. Lee To: S. Sickafuse, L. Pai-Scherf	Proposed revisions to CA225006 and CA225014	4
10/1/2002	TCR	From: L. Lee To: G. Mills, L. Pai-Scherf	Follow-up on the fax to the IRC amendment	4
10/1/2002	TCR	From: L. Lee To: G. Mills, L. Pai-Scherf	Expanded Access Program(EAP)	4
10/2/2002	Amendment 334	G. Jones	IND Safety Report (02/02/01250) Dear Doctor letter - Safety Report previously submitted 9/25 w/o DDL. **Memo attached dating signature obtained from 9/30/02 for submission of DDL to IND	4
10/2/2002	Amendment 335	G. Jones	Protocol Amendment: New Investigator (CA225004;	4
10/2/2002	Fax	From: L. Lee To: P. Delaney via S. Kazmi	EAP (same fax sent to and on 10/1)	4
10/3/2002	TCR	From: L. Pai-Scherf To: N. Mehta	Feedback on Protocol CP02-0144	4
10/7/2002	TCR	From: L. Pai-Scherf To: N. Mehta	Feedback on Protocol CA225006/014	4
10/9/2002	Amendment 336	G. Jones	SAE Initial 15-Day Report (02/02/01283) with	4
10/9/2002	Fax	From: N. Mehta To: L. Pai-Scherf	List of attendees from the 10/9/02 telecon on feedback from Protocols 006 and 014	4
10/10/2002	Fax	From: L. Pai-Scherf To: L. Lee	Summary of 10/9/02 telcon on Protocols 006 and 014	4
10/11/2002	Amendment 337	G. Jones	IND Safety Report 15 Day IND Safety Report Follow-up Mfg. Control #02/02/-1250(1)	4
10/16/2002	Letter	From: S. Sickafuse To: L. Lee	September 17, 2002 - Meeting Minutes (as recorded by FDA)	4
10/18/2002	Amendment 338	G. Jones	Protocol Amendment: New Investigator (0144-	4
10/18/2002	TCR	From: L. Pai-Scherf To: L. Lee	FDA to provide feedback on 0144 CRFs	4
10/23/2002	Amendment 339	G. Jones	General Correspondence: 9/27 fax of 9/25 teleconference attendees; 10/1 fax of EAP outline, 10/1 fax of proposed revisions to 006 and 014	4

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Date	Type	Addressee	Subject	Binder #
10/25/2002	Amendment 340	G. Jones	Request for Special Protocol Assessment: Clinical Studies CA225006 and CA225014	4
10/31/2002	Amendment 342	G. Jones	Other: IRC Charter - Amendment 1	4
10/31/2002	Amendment 341	G. Jones	Protocol Amendment: Change in Protocol (CA225004 and CA225005); Protocol Amendment: New Investigator (CA225004-	4
10/31/2002	Fax	To: G. Mills From: L. Lee	Record of conversation on the IRC Charter	4
11/4/2002	Amendment 343	G. Jones	IND Safety Report - 15 Day IND Safety Report Follow-Up Mfg. Control #02/02/01193 (3)	4
11/13/2002	Amendment 344	G. Jones	Protocol Amendment: CP02-0144 Protocol Amendment 01 CP02-0144 Pharmacokinetics Companion Protocol	4
11/21/2002	Amendment 345	G. Jones	Protocol Amendment: New Investigator (CP02-0144-	4
11/22/2002	Amendment 346	G. Jones	Information Amendment - CMC (DP-02C00203, DS-02J00036)	4
11/22/2002	Facsimile	To: L. Pai-Scherf, S. Sickafuse From: L. Lee	7-Day Notification, Mfg. Control Number 02/02/01350-	4
11/27/2002	Amendment 347	G. Jones	IND Safety Report-15-Day Initial Report (Mfg. Control No. 02/02/01350)-	4
12/4/2002	Amendment 348	G. Jones	Protocol Amendment: New Protocol - CA225041 (Expanded Access Program)	4
12/10/2002	Fax - 349 (see below)	S. Sickafuse	Via fax: Amendment to Special Assessment Protocol: CA225006 & CA225014 for Serial #349	4
12/17/2002	Fax	From: L. Lee To: Lee pai Scherf	Attached proposal for addressing FDA's suggestion regarding the EAP	4
12/17/2002	TCR	From: L. Lee To: S. Sickafuse	Special Protocol Assessment for CA225006 and CA225014	4
12/19/2002	Amendment 350	G. Jones	Information Amendment: Chemistry, Manufacturing and Controls - Lot release for cetuximab Drug Product 02C00063 and 02C00292B	4
12/19/2002	Amendment 351	G. Jones	Protocol Amendment: New Investigator (CP02-0144: CA225004:	4
12/20/2002	Fax	To: Dr. J. Schatcher, G. Mills, Ms. Pat Delaney Sickafuse From: L. Lee	ImClone & BMS Proposal to FDA on the EAP	4
12/23/2002	Amendment 352	G. Jones	Information Amendment: Chemistry, Manufacturing and Control	4
12/24/2002	Amendment 349	G. Jones	Amendment to Request for Special Protocol Assessment: Clinical Studies CA225006 and CA225014	4
12/24/2002	Amendment 353	G. Jones	Detailed Statistical Analysis Plan CP02-9923, CP02-0141, EMR 62 202-007	4

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Date	Type	Addressee	Subject	Binder #
12/24/2002	Amendment 354	G. Jones	General Correspondence: December 10, 2002 facsimile December 17, 2002 facsimile December 20, 2002 facsimile	4
1/2/2003	Fax	From: G. Jones To: L. Lee	Fax indicating IND Amendment #340 - Request for Special Protocol Assessment (SPA) for Protocol CA225014 is incomplete as discussed during the 12/6/02 telcon.	5
1/13/2003	Amendment 355	G. Jones	Request Special Protocol Assessment for: CA225014 (CA225014 v3.0, Monitoring Plan, SAP CA225014, DSMB Charter, Final revised IRC, CRF, Informed Consent	5
1/14/2003	Amendment 356	G. Jones	New Protocol: CA225009 New Protocol: CA225012	5
1/14/2003	Fax	From: L. Lee To: G. Jones	Cover Letter for Serial #355. Special Protocol Assessment for Clinical Protocol CA225014	5
1/15/2003	Amendment 357	G. Jones	Protocol Amendment: New Investigator (CA225041,	5
1/16/2003	Fax	From: L. Lee To: S. Sickafuse	List of attendees from 12/6/02 Teleconference	5
1/23/2003	Amendment 358	G. Jones	General Correspondence: Status Update on Efforts to Address RTF Issues	5
1/23/2003	Fax	From: L. Lee To: S. Sickafuse	Serial No. 358 faxed to	5
1/27/2003	Fax	From: S.Sickafuse To: L. Lee	SPA - not complete and not eligible at this time	5
1/29/2003	TCR	From: S. Sickafuse To: NM, LL	Follow-up to status update on efforts to address RTF issues	5
1/31/2003	Letter	From: G. Jones To: L. Lee	Letter dated 1/24/03 indicating IND Amendment #340 - Request for Special Protocol Assessment (SPA) for Protocol CA225006 is incomplete and not eligible for SPA at this time.	5
1/31/2003	TCR	From: N. Mehta To: G. Mills	SAS Data for Imaging Submission	5
2/3/2003	Amendment 359	G. Jones	Protocol Amendment: New Investigator (CP02-0144: CA225041: CP02-0144 PK Companion:	5
2/3/2003	Fax	From: L. Lee To: G. Mills	Dial-in information for 2/5/2003 telecon and Pre-mtg documentation	5
2/5/2003	Fax	From: L. Lee To: G. Mills	List of attendees from 2/5/2003 teleconference	5
2/6/2003	Amendment 360	G. Jones	(dated 2/5 but not sent via UPS until 2/6) 15-Day IND Safety Report Mfg. Control No. 03/02/01440	5
2/6/2003	Fax	From: D. Lynch To: S. Sickafuse	15-Day IND Safety Report Mfg. Control No. 03/02/01440	5
2/6/2003	Fax	From: L. Lee To: P. Delaney	Copy of press release announcing Expanded Access Program	5
2/6/2003	TCR	From: N. Mehta To: G. Mills	Discussion of the clinical studies: 9923, 0141, 007	5

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Date	Type	Addressee	Subject	Binder #
2/12/2003	Fax	From: L. Lee To: L. Scherf	Request for input on Safety Narratives	5
2/14/2003	Fax	From: L. Lee To: Sharon Sickafuse & Lee Pai Scherf	7-Day Notification received 2/10/2003 follow-up information to the report of submitted on 2/6/2003	5
2/15/2003	TCR	From: L. Lee To: G. Mills, L. Pai-Scherf	Format and requirements for safety narratives	5
2/19/2003	Fax	From: L. Lee To: G. Mills, L. Scherf	Meeting Minutes from 2/14/03 teleconference	5
2/20/2003	E-Mail	From: L. Lee To: G. Mills, L. Pai-Scherf	Regarding ImClone's response to issue of definitions of	5
2/20/2003	Fax	From: L. Lee To: G. Mills, L. Scherf	Point-to-Point response regarding SPA Protocol CA225014	5
2/20/2003	Fax	From: L. Lee To: G. Mills, L. Scherf	Dial-in information for 2/21/03 teleconference on Protocol CA225014	5
2/21/2003	Amendment 361	G. Jones	IND Safety Report Follow-up Mfg. Control No. 03/02/01440 (1)	5
2/21/2003	Amendment 362	G. Jones	Information Amendment: CMC Lot release information Lot No. 02C00062	5
2/21/2003	TCR	L. Scherf	Discussion re: proposal to address FDA's concerns on CA225014 Special Protocol Assessments	5
2/25/2003	Amendment 363	G. Jones	Sent via e-mail on Zip files to be followed up with hard copies on 2/26/03	5
2/25/2003	E-Mail	From: L. Lee To: G. Mills, L. Pai-Scherf	SPA CA225014; zip files containing response to FDA for 014, cover letter for 363, 2/21/2001 TCR, 2/20/2003 fax	5
2/26/2003	Amendment 364	G. Jones	Agreement on format and requirements for safety narratives	5
2/27/2003	E-Mail	From: L. Lee To: G. Mills, L. Pai-Scherf	Dial-in information for 2/27/03 telcon on Minimum duration of prior CPT-11	5
2/27/2003	Fax	From: L. Lee To: G. Mills, L. Pai-Scherf	Dial-in information for 2/27/03 telcon on Minimum duration of prior CPT-11	5
2/28/2003	Amendment 365	G. Jones	Outline of Clinical & Pre-Clinical Rationale for Combination therapy of Cetuximab &	5
2/28/2003	Amendment 366	G. Jones	Status Report on PK Issues -Protocol EMR 62 202-012 -SAP for Integrated PK Analysis	5
2/28/2003	Fax	From: G. Jones To: L. Lee	SPA letter from FDA on Protocol CA225014	5
2/28/2003	Fax	From: L. Lee To: L. Pai-Scherf	Attendees List from 2/27/03 teleconference regarding	5
2/28/2003	TCR	From: L. Lee To: G. Mills, L. Pai-Scherf	FDA's feedback on ImClone's proposal regarding mimimum prior	5
3/3/2003	Amendment 367	G. Jones	Status of On-going Studies	5

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Date	Type	Addressee	Subject	Binder #
3/4/2003	Amendment 368	G. Jones	Protocol Amendment: New Investigator (0144- [replaces Anderson], PK 0144- ; CA225014- CA225041 ; CP02-0144 Monitoring Plan	5
3/10/2003	Amendment 369	G. Jones	Request Special Protocol Assessment for: CA225006 (CA225006 v3.0, Monitoring Plan, SAP CA225006, DSMB Charter, Final revised IRC, CRF, Informed Consent	5
3/10/2003	Fax	G. Jones	BB IND Serial No. 369 Cover Letter Faxed to FDA - Request Special Protocol Assessment for: CA225006	5
3/10/2003	Letter	From: G. Jones To: L. Lee	Request for Special Protocol Assessment to amendment Protocol CA225014	5
3/11/2003	Amendment 370	G. Jones	Information Amendment: CMC (report of investigation of cetuximab drug product lot number 01C00098)	5
3/14/2003	Amendment 371	G. Jones	Protocol Amendment: New Investigator (0144- ; PK for 0144	5
3/18/2003	TCR	From: L. Lee To: G. Mills, L. Pai-Scherf	Response to ImClone's proposal submitted on March 9 (facsimile) for resolution of definition of minimum	5
3/19/2003	Fax	From: L.Lee To: G. Mills, L. Pai-Scherf	Teleconference Meeting Minutes From 3/18/03	5
3/19/2003	Letter	From: G. Jones To: L. Lee	Letter dated 3/14/2003 regarding Proposal to define adequate exposure CP-020023, CP-020141 and EMR-007	5
3/20/2003	Amendment 372	G. Jones	Protocol Amendment: New Investigator (0144- updated 1572 for ; PK for 0144- CA225014- CA225041- , CA225041	5
3/21/2003	Amendment 373	G. Jones	Request for a Clinical Guidance Meeting with the Agency.	5
3/21/2003	Fax	To: S. Sickafuse From: L. Lee	BB IND Serial No. 373 Cover Letter Faxed to FDA - Requesting a Clinical Guidance Meeting with the Agency. (failed attempt on 3/20/2003)	5
3/25/2003	Amendment 374	G. Jones	Information Amendment- Chemistry, Maufacturing, and Controls (lot release for lot no. 02C00292A)	5
3/26/2003	Amendment 375	G. Jones	IND Safety Report- 15-Day Report. Mfg. Control #03/02/01481 (IND Safety Report - 15-Day Report Mfg. Control #03/02/01484 (	5
3/26/2003	TCR	From: N. Mehta To: C. Fuchs	Discussion on the status of lot number 01C00098 associated with cluster of AEs	5
3/27/2003	Fax	From: E. McFadden To: L. Lee	Meeting Confirmation: June 5, 2003	5
3/31/2003	Amendment 376	G. Jones	Annual Report (reporting period December 2001 - December 2002)	5

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Date	Type	Addressee	Subject	Binder #
3/31/2003	Amendment 377	G. Jones	General Correspondence: Agreement on Definition of Minimum Prior Irinotecan	5
4/1/2003	Amendment 378	G. Jones	SAP(and Independent Review Committee Carter) CP02-0144	5
4/1/2003	Fax	To: S. Sickafuse & L. Scherf From: L. Lee	Revised List of questions regarding the protocol, protocol design, study conduct, study goals and data analysis	5
4/7/2003	Amendment 379	G. Jones	Investigator Brochure Version 9.0	5
4/7/2003	E-mail	From: L. Lee To: G. Mills, L. Scherf	Dial-in information for telcon held on 4/8/03 on SPA CA225006	5
4/7/2003	TCR	To: Dr. Chan Fuchs From: N. Mehta	Discussion on the status of lot number 01C00098	5
4/8/2003	Fax	From: L. Lee To: G. Mills, L. Scherf	List of attendees from the 4/8/03 telcon on SPA CA225006	5
4/11/2003	Letter	G. Jones	Additional copies of IND amendment 379 as requested	5
4/14/2003	Amendment 380	G. Jones	General Correspondence: Letter of Authorization to FDA for , MD	5
4/16/2003	Amendment 381	G. Jones	IND Safety Report - 15 Day Report. Mfg. Control #02/02/01342	5
4/16/2003	TCR	To: Dr. Chan Fuchs From: N. Mehta	Discussion of the status of lot number 01C00098	5
4/17/2003	Amendment 382	G. Jones	Statistical Analysis Plan: EMR 62 202-007, CP02-9923, CP02-0141	5
4/18/2003	Amendment 383	G. Jones	SPA Clinical Protocol C225006	5
4/21/2003	Amendment 384	G. Jones	IND Safety Report - 15 Day Report. Mfg. Control # 03/02/01490 (	5
4/21/2003	Amendment 385	G. Jones	Amendment to Request for Special Protocol Assessment: Revised IRC Charter for CA225006	5
4/21/2003	Fax	G. Jones	Revised section 4.4.5 of Final IRC Charter	5
4/21/2003	Fax	To: S. Sickafuse From: L. Lee	IND Safety Report - 15 Day Report. Mfg. Control # 03/02/01490 (	5
4/23/2003	Amendment 386	G. Jones	IND Safety Report - 15 Day Report. Mfg. Control # 03/02/01499 (	5
4/23/2003	TCR	To: Chana Fuchs From: N. Mehta	Discuss BB36 Process/Comparability Amendment and 007 Supply	5
4/23/2003	TCR	Dr. Lee Pai Scherf	Discuss Status of	5
4/25/2003	Amendment 387	G. Jones	Revised Protocols: CA225009, CA225012 Protocol Amendment: New Investigator (CA225014-CA225041 CP02-0144- CP02-9932	5
4/29/2003	Amendment 388	G. Jones	General Correspondence - Copy of fax that contained a list of questions regarding CA225006 submitted as IND amendment 385	5
4/29/2003	Letter	To: Dr. Lily Lee From: G. Jones	FDA Responses to list of questions regarding CA225006 submitted as IND amendment 385	5
5/2/2003	Amendment 389	G. Jones	Protocol Amendment: New Investigator (CA225012	5

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Date	Type	Addressee	Subject	Binder #
5/6/2003	Amendment 390	G. Jones	Information Amendment: Chemistry, Manufacturing, and Control Toxin Investigation in Lot 01C00098	5
5/8/2003	Amendment 391	G. Jones	FDA Clinical Guidance Mtg. June 5, 2003 Pre-Meeting Package - Includes: Executive Summary, Addressing the Refusal-to-File Issues, Questions to FDA, Pre-clinical and Clinical Rationale, and Appendices	5
5/9/2003	Amendment 392	G. Jones	Protocol Amendment: New Protocol CA225006 New Investigator CA225006 CA225014 , CA225041 (	5
5/12/2003	Amendment 393	G. Jones	Attachments (tables and figures) for Rationale of Combination Treatment contained in Serial No. 391 (Pre-Meeting Package)	5
5/13/2003	TCR	To: Sharon Sickafuse From: Dr. Lily Lee	Confirm receipt of the June 5th pre-meeting package	5
5/13/2003	Amendment 394	G. Jones	Letter	5
5/14/2003	Amendment 395	G. Jones	March 20, 2003 Meeting Minutes: Demo for Imaging Submission	5
5/16/2003	Amendment 396	G. Jones	Partial Clinical Hold - ImClone's Complete Response to FDA Comments	5
5/22/2003	Amendment 397	G. Jones	IND Safety Report- 15-day Follow-up Report Mfg. Control #03/02/01481(1)	5
5/22/2003	Fax	To: Dr. Martin Green, Sharon Sickafuse From: Dr. Lily Lee	Synopsis of Results for Pharmacokinetics and Pharmacodynamics Studies CA225004 and CA225005	5
5/22/2003	Fax	To: Dr. Patricia Keegan From: Dr. Lily Lee	Time and Location of Erbitux Presentations and Poster Outlines for ASCO 2003	5
5/22/2003	Fax	To: S. Sickafuse & L. Scherf From: L. Lee	IND Safety Report - 7-Day Notification Mfg. Control # 03/02/01497	5
5/22/2003	TCR	To: Dr. Lee Pai Scherf From: Dr. Lily Lee	To discuss Pre-June 5th Meeting Preparation with	5
5/27/2003	Amendment 398	G. Jones	CA225004 and CA225005 Clinical Study Reports	5
5/27/2003	Fax	To: Dr. L. Pai-Scherf, Dr. G. Mills, Dr. M. Green, cc:Sharon Sickafuse From: Dr. Lily Lee	Overview of Content and Structure of the Clinical/Statistical Section Module 5 of CTD	5
5/28/2003	Amendment 399	G. Jones	Copy of Fax Sent 2/27/03 Regarding the Content and Structure of the Clinical/Statistical Section Module 5 of CTD	5
5/29/2003	Amendment 400	G.Jones	IND Safety Report Clarification Mfg. Control # 03/02/01497 (Change in Investigator Causality Assessment)	5
5/29/2003	Fax	To: Dr. L. Pai-Scherf From: Dr. Lily Lee	List of Investigators, Affiliations, and Number of Patients Enrolled in Each Site and List of Protocol Deviations for EMR-007 Study	5

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Date	Type	Addressee	Subject	Binder #
5/30/2001 & 6/1/03	Summary of Discussions	To: Lee Pai-Scherf and Pat Keegan From: Dr. Lily Lee	Summary of Discussions held at ASCO Regarding Content and Structure of BLA	5
6/5/2003	Fax	To: Dr. L. Pai-Scherf From: Dr. Lily Lee	List of response rates by clinical sites for study EMR-007	5
6/6/2003	Amendment 402	G.Jones	Protocol Amendment (PG): CA225014 Monitoring Plans: CA225004 and CA225005 New Investigator CA225006 CA225014 CA225041	5
6/6/2003	Fax	To: S. Sickafuse From: Dr. Nikhil Mehta	Request for a Pre-BLA CMC Teleconference	5
6/9/2003	Amendment 403	G.Jones	Copy of Fax Which Contains an Overview of the Content and Structure for the Clinical/Statistical Section of Module 5 of the CTD	5
6/9/2003	Amendment 404	G.Jones	IND Safety Report - 15 Day Report Mfg. Control #03/02/01505	5
6/10/2003	Amendment 401	G.Jones	Special Protocol Assessment Modification and Revised IRC Charter for CA225014	5
6/10/2003	Amendment 401-Fax	G. Jones	Duplicate Cover Letter of Serial No. 401- Special Protocol Assessment Modification and Revised IRC Charter for CA225014	5
6/10/2003	Amendment 405	G. Jones	Information Amendment: Chemistry, Manufacturing, and Control - Lot Release Documentation for Lot No. 02C00486	5
6/11/2003	Fax	To: Sharon Sickafuse From: Dr. Lily Lee	Duplicate cover letter of Serial No. 396 (Partial Clinical Hold-Complete Response-i as requested by the Agency	5
6/12/2003	Fax	To: Dr. Chana Fuchs From: Dr. Lily Lee	Incidence of CA225041(EAP Protocol)	5
6/12/2003	Fax	To: Dr. Lee Pai Scherf From: Dr. Lily Lee	Incidence of CA225041(EAP Protocol)	5
6/13/2003	Email	To: Dr. Lee Pai Scherf From: Dr. Lily Lee	Incidence of CA225041(EAP Protocol)	5
6/16/2003	Amendment 406	G. Jones	Final Clinical Study Report for EMR 62 202-007	5
6/16/2003	Email	To: Dr. Lee Pai Scherf From: Dr. Lily Lee	Information to facilitate arrangement for Clinical Site Audits (CP02-9923, CP02-0141, EMR 62 202-007)	5
6/17/2003	Amendment 407	G. Jones	Information for Clinical Site Audits (CP02-9923, CP02-0141, EMR 62 202-007) and copies of faxes previously sent pertaining to EMR 62 202-007	5
6/19/2003	Amendment 408	G. Jones	Information Amendment- Chemistry, Maufacturing, and Controls (Lot Release Information for Lot No. 02C00673)	5
6/18-6/19/03	TCR	To: Dr. Lee Pai Scherf From: Lily Lee	Comments on the Reviewer's data base	5
6/18/2003	Email	To: Dr. Lee Pai Scherf From: Lily Lee	Proposed structure of reviewer's data base	5

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Date	Type	Addressee	Subject	Binder #
6/20/2003	Letter	G. Jones	FDA Response re Partial Clinical Hold (Clinical Hold Removed)	5
6/20/2003	Fax	To: Sharon Sickafuse From: Dr. Lily Lee	ImClone Minutes and Presentation from June 5, 2003 FDA Meeting	5
6/20/2003	Fax	To: Nik Mehta From: Emily McFadden	FDA Confirmation of Pre-BLA CMC Teleconference - scheduled for July 31, 2003	5
6/20/2003	Email	To: Dr. Lee Pai Scherf From: Lily Lee	007 Zip File, Protocol and Amendment	5
6/24/2003	Amendment 409	G. Jones	Pre-BLA CMC Meeting package	5
6/24/2003	Email	To: Dr. Lee Pai Scherf and Dr. George Mills From: Dr. Lily Lee	Revised document for the reviewers database that includes: an Executive Summary and a Detailed Description of Each Data Set	5
6/24/2003	Email	To: Dr. Lee Pai Scherf and Dr. George Mills From: Dr. Lily Lee	Dial in information for Reviewers Database Teleconference	5
6/24/2003	Letter	To: L. Lee From: FDA	Transfer of IND FDA Review and Oversight from CBER to CDER	5
6/25/2003	Fax	To: Dr. Lee Pai Scherf From: Dr. Lily Lee	Request for Information from EMR-007 for Clinical Site Audit	5
6/25/2003	Email	To: Dr. Lee Pai Scherf From: Lily Lee	BOND Study Report	5
6/27/2003	Amendment 410	G. Jones	New Investigator CA225006 CA225014 CA225041 (Fuloria) Investigator Documentation CA225014 , CA22504	5
7/1/2003	Amendment 411	G. Jones	Additional copies of Pre-BLA CMC Pre-Meeting Package (Serial No. 409) as Requested by	5
7/1/2003	Letter	To: L. Lee From: FDA	FDA Memo (minutes) of June 5, 2003 meeting	5
7/8/2003	Amendment 412	G. Jones	e-BLA demo	5
7/11/2003	Amendment 413	G. Jones	General Correspondence: Sponsor's minutes to the June 5, 2003 FDA meeting, (EMR-007), Agreement on Structure of Reviewer's Data Base	5
7/18/2003	Amendment 414	G. Jones	General Correspondence: Documents regarding the observation of : CA225041	5
7/18/2003	Amendment 415	G. Jones	General Correspondence: DLT for BLA Test Load	5

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7/28/2003	Amendment 416	G. Jones	- Protocol Amendment: New Investigators CA225006 CA225012 ; CA225014 CA225041 CP02-0144 - CA225041 Protocol Amendment 01& 02 - CA225041 Revised Protocol 01	5
7/30/2003	Fax	To: S. Sickafuse From: N. Mehta	Dial in information for CMC Pre-BLA Teleconference and list of attendees	5
7/30/2003	Amendment 417	G. Jones	IND Safety Report- 15-day Follow-up Report Mfg. Control #03/02/01440 (2) IND Safety Report- 15-day Follow-up Report Mfg. Control #02/02/01093 (2)	5
8/8/2003	Amendment 418	G. Jones	Justification for FDA Image Review Station Hardware Upgrade	6
8/8/2003	Amendment 419	G. Jones	General Correspondence: Cross-Reference Letter Authorization for to use IND for the Compassionate Treatment of (	6
8/8/2003	Fax	To: G. Mills From: L. Lee	Proposed schedule for delivery and tutorial for ERBITUX BLA Medical Imaging Review	6
8/8/2003	Fax	To: M. Fauntleroy From: L. Lee	Rationale for Upgrade of Imaging Review System Hardware	6
8/8/2003	Fax	To: G. Mills From: L. Lee	Rationale for Upgrade of Imaging Review System Hardware	6
8/11/2003	Fax	To: G. Mills From: L. Lee	Discussion on Proposal to Upgrade FDA's Imaging and Review System	6
8/11/2003	Fax	To: M. Fauntleroy From: L. Lee	Discussion on Proposal to Upgrade FDA's Imaging and Review System	6
8/11/2003	Letter	To: L. Lee From: Earl Dye for Glen Jones	Response to the June 10, 2003 submission which contained revisions to protocol CA225014 and to the IRAC charter that reflect the comments provided by the FDA in review of clinical protocol CA225006, in which protocol CA225014 was accepted for Special Protocol Assessment.	6
8/14/2003	TCR	To: R. Levin From: L. Lee	Discussion surrounding ImClone's proposal to upgrade FDA's hardware and software for radiology review system	6
8/20/2003	Fax	To: Sharon Sickafuse/Monica Hughes From: N. Mehta	List of Attendees and their titles at the July 31st CMC Pre-BLA Teleconference for cetuximab	6

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8/21/2003	Amendment 420	G. Jones	IND Safety Report- 15-day Follow-up Report Mfg. Control #03/02/01505 (1) (Update of Amendment 404 -	6
8/26/2003	Amendment 421	G. Jones	New Investigator: CA225006 Revised 1572: CA225041 ( ), CP02-0144	6
8/28/2003	Letter	From: FDA To: L. Lee	Copy of memorandum from July 31, 2003 telephone conversation between ImClone Systems and FDA regarding :	6
9/17/2003	TCR	To: Lily Lee From: Dr. P. Keegan	Request for Investigator IND and review status	6
9/23/2003	Amendment 422	G. Jones	CA225009: Revised protocol No. 02 (dated 5/1/03), Revised protocol No. 03 (dated 5/12/03), and Revised protocol No. 04 (dated 7/8/03) Administrative Letters dated 5/10/03 and 7/8/03, Monitoring Plan, New Investigator: New Investigator: CA225006 Revised 1572: CP02-0144	6
9/24/2003	Amendment 423	G. Jones	General Correspondence: Reference Letter for Physician Sponsored IND	6
9/24/2003	TCR	To: Dr. Pat Keegan and Lee Pai Scherf From: Lily Lee	Follow-up regarding Investigator INDs and EAP program	6
9/25/2003	Amendment 424	G. Jones	Special Protocol Assessment: CA225014	6
9/25/2003	Amendment 425	G. Jones	Special Protocol Assessment: CA225006 (Study specific questions, Revised protocol, Informed Consent template, Revised IRC Charter 3.0)	6
9/29/2003	Amendment 426	G. Jones	General Correspondence: Reference Letter	6
10/1/2003	Amendment 427	G. Jones	General Correspondence: Reference Letter	6
10/6/2003	TCR	To: George Mills From: Debbie Lynch	Disussion regarding IRC Charters for CA225006 and CA225014	6
10/10/2003	TCR	To: Sharon Sickafuse From: Debbie Lynch	Physician Sponsored IND Applications:	6
10/14/2003	Amendment 429	G. Jones	Protocol Amendment: New Investigator CA225006 , CA225012	6
10/15/2003	Amendment 428	G. Jones	IND Safety Report – 15-Day Report Mfg. Control #12394664	6

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10/15/2003	TCR	To: Karen Jones From: Debbie Lynch	Tabular listing of all revisions to clinical protocols CA225006 and CA225014	6
10/15/2003	TCR	To: Lee Pai-Scherf From: D. Lynch and P. Molloy	IND Safety Report for Protocol CA225041	6
10/16/2003	TCR	To: Monica Hughes From: Debbie Lynch	CA225014 Protocol Revision Summary and Physician Sponsored IND Applications	6
10/17/2003	E-mail	To: G. Mills From: L. Lee	Revised IRC Charter Study CA225006	6
10/17/2003	TCR	To: Debbie Lynch From: Mary Andrich	Confirmed receipt of Revised IRC Charter Study CA225006	6
10/21/2003	Amendment 430	G. Jones	IND Safety Report – 15-Day Report Mfg. Control #03/02/01954	6
10/22/2003	TCR	To: Lily Lee From: Dr. U and Jose Tavarez	Details of the Clinical Site Audit	6
10/23/2003	Amendment 431	G. Jones	General Correspondence:	6
10/23/2003	Fax	To: Lee Pai Scherf From: Debbie Lynch	Identification of Protocol Changes for Studies CA225014 and CA225006	6
10/28/2003	Amendment 432	G. Jones	General Correspondence: Reference Letter	6
10/30/2003	Amendment 433	G. Jones	IND Safety Report – 15-Day Report Mfg. Control #02/02/01051 - Mfg. Control #12394664(1) - follow-up report	6
10/31/2003	TCR	To: Sharon Sickafuse From: Debbie Lynch	Physician Sponsored IND	6
11/4/2003	Amendment 434	G. Jones	Protocol Amendment: New Protocol CA225020 (E8200) Protocol Amendment: New Investigators CA225020 (E8200):	6
11/4/2003	TCR	To: Lee Pai Scherf & Mark Thornton From: L. Lee	Request for Information: Studies with BB36 material, Pulmonary AEs; Inquiry regarding ODAC	6
11/7/2003	Amendment 435	G. Jones	Protocol Amendment: New Investigators CA225006: EMR 62 202-025:	6
11/7/2003	Amendment 436	G. Jones	Information Amendment - Chemistry, Manufacturing and Controls (Lot release information for Drug Product Lot 02C01149 and the bulk drug substance Lot No. 02J00265)	6
11/13/2003	Amendment 437	G. Jones	IND Safety Report – 15-Day Follow-up Report Mfg. Control #02/02/01051 - follow-up report	6
11/18/2003	Email	To: Lee Pai Scherf From: L. Lee	Confirmation for Telecon on 11/19/2003	6

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11/19/2003	Email	To: Lee Pai Scherf From: L. Lee	Attendees from 11/19/03 teleconference	6
11/21/2003	Amendment 438	G. Jones	General Correspondence: Reference Letter	6
12/2/2003	Email	To: Lee Pai Scherf From: Lily Lee	Update of Adverse Reaction Section of PI	6
12/2/2003	Email	To: Lee Pai Scherf From: Lily Lee	Update of Adverse Reaction Section of PI - Administrative Information	6
12/2/2003	Email	To: Lily Lee From: Lee Pai Scherf	FDA Attendee List from 12/5/03 Telcon	6
12/8/2003	Amendment 439	G. Jones	Protocol Amendment: New Investigators CA225006: 62 202-025: CA225012: CA225014: CA225020 (E8200): CP02-0036: CP02-0141:	6
12/8/2003	Amendment 440	G. Jones	General Correspondence: National Cancer Institute Cross Reference letter	6
12/9/2003	Amendment 441	G. Jones	Protocol Amendment: New Protocol CA225045 Protocol Amendment: New Investigator -	6
12/17/2003	Amendment 442	G. Jones	Protocol Amendment: New Investigator CA225006: EMR 62 202-025: CA225020 (E8200): CA225045:	6
12/17/2003	Amendment 443	G. Jones	Information Amendment - Chemistry, Manufacturing and Controls (Lot release information for Drug Product Lot 03C00036 and the bulk drug substance Lot No. 200181)	6
12/22/2003	Letter	To: Lily Lee From: Earl Dye	FDA Response to Special Protocol CA225014 Revisions submitted	6
12/22/2003	Letter	To: Lily Lee From: Earl Dye	FDA Response to Special Protocol CA225006 Revisions submitted	6
12/23/2003	Amendment 444	G. Jones	General Correspondence: Cross Reference Letter	6
12/30/2003	Amendment 445	G. Jones	SPA Modification: Clinical Protocol CA225014 includes revised DSMB Charter, revised IRC Charter and revised protocol 05	6
1/5/2004	Amendment 446	G. Jones	Notification of ImClone Systems' Address Change	6

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Date	Type	Addressee	Subject	Binder #
1/9/2004	Amendment 447	G. Jones	Special Protocol Assessment: Protocol CA225006, a list of items being submitted for SPA Review, and questions regarding CA225006 Clinical Protocol and IRC Charter	6
1/12/2004	Amendment 448	G. Jones	Protocol Amendment: New Investigators EMR 62 202-025: CA22501: CA225020 (E8200): CA22504: CA225045: CP02-0144:	6
1/20/2004	Amendment 449	Glen Jones	Information Amendment - Chemistry, Manufacturing and Controls Notification of Osmolality and IEF specification changes	6
1/23/2004	E-mail	To: Lee Pai-Scherf From: Lily Lee	Study-014 DSMB Recommendation	6
1/26/2004	Amendment 450	Glen Jones	General Correspondence: Reference Letter	6
1/27/2004	Amendment 451	Glen Jones	Special Protocol Assessment: Protocol CA225014 Data Safety Monitoring Board Results	6
1/29/2004	E-mail	To: Sharon Sickafuse and Lee Pai-Scherf	Study-014 DSMB Package	6
2/3/2004	Amendment 452	Glen Jones	General Correspondence Cross Reference Letter	6
2/3/2004	Amendment 453	Glen Jones	General Correspondence: Cross Reference Letter for BMS Study CA225059	6
2/9/2004	Amendment 454	Glen Jones	Information Amendment - Chemistry, Manufacturing and Controls (Lot release information for Drug Product Lot No. 03C00516 and the bulk Drug Substance Lot No. 201400)	6
2/10/2004	Amendment 455	Glen Jones	IND Safety Report - 15 Day [Mfg. #04/02/02202 & 04/02/02170]	6
2/10/2004	Amendment 456	Glen Jones	Post Marketing of Adverse Drug (mfr #12495933)	6
2/13/2004	Amendment 457	Glen Jones	Protocol Amendment: New Investigators : EMR 62 202-025: CA225020 (E8200): CA225041: : CP02-0144:	6
2/13/2004	Amendment 458	Glen Jones	IND Safety Report - 15 Day Report [Mfg. Control #12497202]	6
2/17/2004	Amendment 459	Glen Jones	General Correspondence: Cross Reference Letter	6

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2/20/2004	Amendment 460	Glen Jones	Protocol Amendment: New Investigators EMR 62 202-025:	6
2/23/2004	Amendment 461	Glen Jones	IND Safety Report - 15 Day Follow-up Report [Mfg. Control #04/02/02202 (1)]	6
2/24/2004	Amendment 462	Glen Jones	General Correspondence: Transfer of Drug Safety Reporting to BMS	6
2/25/2004	Amendment 463	Glen Jones	IND Safety Report - 15 Day Report [Mfg. Control #12494035] IND Safety Report - 15 Day Report [Mfg. Control #12488326] IND Safety Report - 15 Day Report [Mfg. Control #12511564]	6
2/27/2004	Amendment 464	Glen Jones	Protocol Amendment: New Investigators CA225006:: CA225014:	6
2/27/2004	Fax	To: Sharon Sickafuse From: Lily Lee	Request for Meeting: Clinical Guidance Meeting with the FDA Clinical Review Team - 4/12-19/04	6
2/27/2004	Amendment 465	Glen Jones	Request for Meeting: Clinical Guidance Meeting with the FDA Clinical Review Team - 4/12-19/04	6
3/2/2004	Fax	From: Emily McFadden To: Lily Lee	Other IND Proposed Meeting: April 29, 2004, in Rockville, MD, from 14:30 -16:00 EST.	6

BLA 2003 Chronological Index of FDA Communications

Date	Type	Addressee	Subject	Binder #
8/6/2003	Letter	FDA Mellon Client Service Center	Check (#082519) for the BLA in the amount of $533,400.00	1
8/12/2003	Other	To: Glen Jones From: L. Lee	Installation of the hard drive/monitors and 49 Image DVDs in office	1
8/14/2003	Letter	To: Glen Jones From: L. Lee	Submission of original BLA application with 49 Image DVDs (Archival Copies)	1
8/21/2003	TCR	To: Monica Hughes From: N. Mehta	Status of STN number and Review Team. STN number not yet assigned, but review team formed.	1
8/22/2003	TCR	To: Monica Hughes From: N. Mehta	STN number to be provided at a later date.	1
8/22/2003	TCR	To: George Mills From: N. Mehta	- Installation of the final validated application for the Imaging Review System on 8/26/03 - Email informing and team of upcoming plans as discussed with	1
8/25/2003	TCR	To: Karen Jones From: N. Mehta	BLA STN number assigned - 125084/0	1
8/26/2003	Other	To: George Mills From: N. Mehta	Installation of the Application CD on the hard drive in office. Additionally, the updated information from Image DVDs #5 and #8 were installed on office system.	1
8/26/2003	Amendment 001	To: Glen Jones From: L. Lee	- Amended Labeling TOC with additional hyperlink to WORD version of proposed package Insert. - Amended CRF TOC with correction to the identification of treatment studies on certain studies.	1
8/26/2003	Other	To: George Mills From: N. Mehta	Review Aid to : - 8/25/03 CD containing responses to request for information (Note: These responses will also be filed to the BLA as amendment 002) - 2 copies of the BioImaging BIB Manual containing User Manual (8/22/03) and IRC Documentation (8/25/03)	1
9/2/2003	Email	To: Sharon Sickafuse From: N. Mehta	Verification that the correct versions of the Amendment 001 TOCs (Labeling and CRF) have been loaded.	1
9/2/2003	Letter	To: L. Lee From: Earl Dye for G. Jones	Official letter stating FDA receipt of BLA, FDA Submission Tracking Number, and intent to review the application for accelerated approval	1
9/3/2003	Amendment 002	To: Glen Jones From: L. Lee	Corrected Labeling TOC	1
9/4/2003	Letter	To: George Mills From: Debbie Lynch	Copy of Reviewers Aid CD and inventory sheet sent per request to his home address	1
9/4/2003	TCR	To: Chana Fuchs From: N.Mehta, L.Lee	Manufacturing Facility Inspections	1
9/5/2003	TCR	To: Sharon Sickafuse From: N. Mehta	Multiple discussions with regarding Amendments 001 and 002.	1

BLA 2003 Chronological Index of FDA Communications

Date	Type	Addressee	Subject	Binder #
9/9/2003	Amendment 003	To: Glen Jones From: L. Lee	- Response to the requests by : Registration Number - Archival copy of the Medical Imaging Review System Application CD installed in : office on August 26, 2003. - Dako cross-reference letter	1
9/9/2003	TCR	To: L. Lee From: Debbie Trout	Inspection of Manufacturing Facilities 1. Nov. 5 to 14, 2003 2. Dec. 1-5, 2003 3. : Still under discussion	1
9/10/2003	TCR	To: Sharon Sickafuse From: L. Lee	Additional Information regarding	1
9/10/2003	Letter	To: Rosa Brown From: L. Lee	Registration of as manufacturer of clinical supplies and as manufacturer of cetuximab.	1
9/11/2003	TCR	To: Chana Fuchs From: N. Mehta	BLA information and Inspection of Manufacturing Facilities	1
9/11/2003	TCR	To: Jose Tavarez From: L. Lee	Clinical Site Audit for BLA	1
9/12/2003	TCR	To: Jose Tavarez From: L. Lee	Information regarding clinical site audits	1
9/12/2003	TCR	To: S. Sickafuse From: L. Lee	Request for database information	1
9/12/2003	Fax	To: L. Lee From: Jose Tavarez	The following sites have been selected for inspection for BLA STN 125084, ERBITUX: - Study 007: - Study 9923: - Notebooks with additional information will be required.	1
9/15/2003	Fax	To: Jose Tavarez From: L. Lee	Response to 9/12/03 fax re: Clinical Site Audit for BLA. Names and contact information for European sites selected for inspection.	1
9/15/2003	Fax	To: Gerry McGirl From: L. Lee	Names and contact information for European sites selected for inspection.	1
9/15/2003	TCR	To: Jose Tavarez and Gerry McGirl From: L. Lee and D. Lynch	Scheduling of Clinical Site Audits	1
9/16/2003	Fax	To: George Mills From: L. Lee	Information requested to identify data variables and databases	1
9/17/2003	Fax	To: Jose Tavarez From: L. Lee	Response to 9/12/03 fax re: Clinical Site Audit for BLA. Names and contact information for CP02-0141 and CP02-9923 sites selected for inspection.	1
9/17/2003	TCR	To: Lily Lee From: Pat Keegan	Request for Investigator IND and review status	1
9/17/2003	Fax	To: Gerry McGirl From: L. Lee	Response to 9/12/03 fax re: Clinical Site Audit for BLA. Names and contact information for CP02-0141 and CP02-9923 sites selected for inspection.	1

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Date	Type	Addressee	Subject	Binder #
9/17/2003	TCR	To: Gerry McGirl From: L. Lee	007 Audit schedule and Site Notebook information	1
9/19/2003	Amendment 004	To: G. Jones From: L. Lee	120-Day Safety Update including Safety Summay/tables/listings for Study IMCL CP02-0144	1
9/19/2003	Email	To: Gerry McGirl From: L. Lee	Inspections/Audits BLA STN 125084	1
9/22/2003	Fax	From: L. Lee To: Gerry McGirl	Hotel Recommendations and Local Authority Addresses	1
9/23/2003	TCR	From: Debbie Lynch To: Jose Tavarez	Confirmed that Clinical Site Notebooks for US sites would be delivered to FDA on September 26, 2003. Also confirmed address to be delivered.	1
9/24/2003	Fax	From: L. Lee To: Jose Tavarez	Hotel Recommendations and Local Authority Addresses	1
9/24/2003	Fax	To: L. Lee From: Jose Tavarez	Information requested in teleconference including additional data needed for foreign sites selected for inspection	1
9/25/2003	Fax	To: Jose Tavarez From: L. Lee	Overall Contact information for Clinical Site Audits for Study EMR 62 202-007 (Dr. Thomas Wenzel)	1
9/25/2003	Letter	To: Jose Tavarez From: L. Lee	Clinical Site Audit Notebooks for: CP02-0141 ?) CP02-9923 ıfel 060,	1
9/26/2003	TCR	To: Debbie Trout From: N. Mehta	Limited inspection to: Follow-up the 2001 inspection and to inspect new lots. Also, Cardinal Inspection team formed	1
9/30/2003	TCR	To: Gerry McGirl From: Debbie Lynch	Clinical Site Notebooks: Confirmed that electronic copies would not be needed and the notebooks were to be shipped directly to FDA inspectors	1
9/30/2003	TCR	To: Jose Tavarez From: Debbie Lynch	confirmed receipt of U.S. Site Notebooks sent 9/25/03. provided that the European Site Notebooks would be sent directly to the FDA investigators the 1st week in October.	1
9/30/2003	Fax	To: Jose Tavarez From: L. Lee	Letters from each of the EMR 62 202-007 principal investigators authorizing the site inspection by FDA and allowing for access to the patient records. Also included was a letter from ImClone confirming that FDA will have access to the patient records.	1
10/1/2003	TCR	To: Sharon Sickafuse From: L. Lee	Carton and vial label and status of BLA review	1
10/1/2003	TCR	To: Debbie Trout From: L. Lee	Proposal for an earlier inspection at :	1
10/2/2003	Letter	To: Sandra Shire From: L. Lee	EMR 62-202 007 Clinical Site Notebooks as requested in the September 12 fax from .	1
10/2/2003	Letter	To: Gerald McGirl From: L. Lee	EMR 62-202 007 Clinical Site Notebooks as requested in the September 12 fax from	1

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Date	Type	Addressee	Subject	Binder #
10/2/2003	Letter	To: Dr. Khin U From: L. Lee	EMR 62-202 007 Clinical Site Notebooks as requested in the September 12 fax from	1
10/9/2003	Amendment 005	To: G. Jones From: L. Lee	1. Identification of the EMR 62-202-007 variables in the database 2. Revised vial and carton label providing lot number and expiration date	1
10/9/2003	TCR	To: S. Sickafuse From: N. Mehta	Status of BLA Review regarding "Acceptable for filing" letter, ODAC decision, and DAKO's filing	1
10/10/2003	Fax	To: L. Lee From: Earl Dye	Fax informing ImClone that FDA has filed BLA and that the user fee goal date is February 13, 2004.	1
10/15/2003	TCR	To: Debbie Trout From: N. Mehta	Status of BLA Review	1
10/17/2003	TCR	To: Gerry McGirl From: Debbie Lynch	Finalized travel plans for upcoming clinical site inspections for EMR 62 202-007.	1
10/20/2003	Letter	To: Lily Lee From: Earl Dye	Letter informing ImClone that FDA has filed BLA and that the user fee goal date is February 13, 2004.	1
10/21/2003	E-mail	To: Gerry McGirl From: Lily Lee	Inspections/Audits BLA STN 125084	1
10/22/2003	TCR	To: Chana Fuchs From: N. Mehta	Preparation for Inspection of Cetuximab Manufacturing Facilities	1
10/22/2003	TCR	To: Jose Tavarez, Dr. U From: L. Lee	Details of Clinical Site Audit	1
10/23/2003	TCR	To: Dr. U and Dr. Lee Pai Scherf From: Lily Lee	Question on randomization scheme for 007 and test dose	1
10/23/2003	Fax	To: J. Tavarez, Dr. U From: L. Lee	BOND Study Report explaining the method of assigning patients to treatment groups.	1
10/24/2003	Fax	To: L. Lee From: S. Sickafuse	Potential Review Issues ("Day 74 Letter")	1
10/28/2003	TCR	To: Sharon Sickafuse From: L. Lee	Clarification of "Day 74 Letter"	1
10/28/2003	TCR	To: Debbie Trout From: N. Mehta	BB36 Inspection	1
10/28 & 10/31	TCR	To: Chana Fuchs From: N. Mehta	Lots manufactured at	1
10/29 and 10/30	TCR	To: Lily Lee From: Lee Pai Scherf	Request for clarifications on HACA data variables	1
10/30/2003	Fax	To: L. Lee From: S. Sickafuse	Potential Review Issues (Replaces previous "Day 74 letter")	1
10/30/2003	Fax	To: Lee Pai Scherf From: L. Lee	Reponse to Request for clarifications in the HACA data set	1
10/31/2003	Fax	To: Chana Fuchs From: N. Mehta	Requested information tables for lots which have been manufactured since the last inspection	1
10/31/2003	Email	To: Chana Fuchs and Debbie Trout From: N.Mehta	Requested BB36 plant policy, manufacturing schedule, and QC schedule	1
11/3/2003	Letter	To: L. Lee From: S. Sickafuse	Potential Review Issues (Replaces previous (Day 74 letter)	1

* TCR- Telecontact Report

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Date	Type	Addressee	Subject	Binder #
11/4/2003	TCR	To: Lee Pai Scherf & Mark Thornton From: L. Lee	Request for Information: Inquiry regarding ODAC	1
11/4/2003	Fax	To: L. Lee From: Mark Thorton	List of patients	1
11/7/2003	Email	To: Chana Fuchs From: N. Mehta	List of deviations associated cetuximab manufacture at	1
11/12/2003	Amendment 006	To: G. Jones From: L. Lee	Response to the first issue identified in the 10/27/03 FDA letter regarding the Dosage and Administration section of the proposed package insert.	1
11/17/2003	TCR	To: Sharon Sickafuse From: L. Lee	Discussion regarding data from BB36 materials	1
11/19/2003	TCR	To: Lee Pai Scherf From: L. Lee	Discussion regarding BB36 PK data	1
11/19/2003	Email	To: L. Lee From: Lee Pai Scherf	Tcon for PK discussion	1
11/21/2003	TCR	To: Sharon Sickafuse From: L. Lee	Updates on status of BLA amendments and reviews	1
11/24/2003	Letter	To: Lee Pai Scherf From: Debbie Lynch	2 CDs containing narratives and supporting documents for the patients with pulmonary adverse events	1
11/24/2003	Fax	To: Dr. U c/o Jose Tavarez From: L. Lee	Update on corrective actions taken at Site 603 in response to observations noted during the FDA inspection on 10/27 - 10/31	1
11/24/2003	Fax	To: Dr. U c/o Jose Tavarez From: L. Lee	Update on corrective actions taken at Site 600 (Van Cutsem) in response to the FDA inspection on 11/3 - 11/6	1
11/25/2003	Fax	To: Lee Pai Scherf From: L. Lee	Lot numbers in Section 3.2.2 of the EMR-007 Study Report	1
11/26/2003	TCR	To: Chana Fuchs From: N. Mehta	PAI, PK, Immunogenicity	1
11/26/2003	TCR	To: Debbie Trout From: N. Mehta	Cardinal PAI requests	1
11/28/2003	E-mail	To: Mark Thornton From: N. Mehta	List of Attendess from 11/25/03 Teleconference	1
11/28/2003	E-mail	To: Chana Fuchs From: N. Mehta	Immunogenicity Report for Staudy 007	1
12/2/2003	E-mail	To: David Green and Lee Pai Scherf From: Lily Lee	Password protected zip file containing the PK data requested during teleconference on November 19, 2003 (password forwarded in separate e-mail). (11:23 a.m.)	1
12/2/2003	E-mail	To: Lee Pai-Scherf and Mark Thornton From: Lily Lee	Dose Modification: Administrative Information (11:52 a.m.)	1
12/2/2003	E-mail	To: Dr. Pai-Scherf and Dr. Thornton From: L.Lee	Password protected zip file containing the dose modification for during teleconference on November 24, 2003 (password forwarded in separate e-mail)	1
12/2/2003	E-mail	To: Lee Pai-Scherf From: L.Lee	Password protected zip file containing the update of the (password forwarded in separate e-mail)	1

* TCR- Telecontact Report

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Date	Type	Addressee	Subject	Binder #
12/2/2003	TCR	To: Sharon Sickafuse From: Lily Lee	Status Updates and Additional Requests for Information re: PK Response, Dose Modification, Revised PI AE section	1
12/3/2003	Amendment 007	To: G. Jones From: L. Lee	Response to October 27, 2003 FDA "Day 74" Letter	1
12/3/2003	Letter	To: Lee Pai-Scherf From: Debbie Lynch	2 CDs containing narratives and supporting documents for the patients Note: CDs were sent via UPS on 11/24/03 but did not make it to l as of 12/2/03 therefore CDs were hand delivered	1
12/4/2003	Amendment 008	To: G. Jones From: L. Lee	Responses to Requests for Information re: 1) PK Response, 2) Correction to EMR 62 202-007 PK Report, 3) Dose Modification, 4) Revision of Patient Narratives 5) Revised PI AE section, 6) Revised Clinical overview	1
12/5/2003	TCR	To: Sharon Sickafuse From: L. Lee	Discuss the BB36 PK Analysis and	1
12/9/2003	TCR	To: N.Mehta From: Debbie Trout	Request to submit information regarding the use of MDL warehouse to the BLA	1
12/8 and 12/9/03	TCR	To: Chana Fuchs From: N.Mehta, L.Lee	BLA Review	1
12/9/2003	TCR	To: Pat Keegan From: L.Lee	Request for face-to-face meeting	1
12/10/2003	Email	To: Lee Pai Scherf From: Lily Lee	Attendee List from 12/5/03 Telcon	1
12/11/2003	Email	To: Lee Pai Scherf From: Lily Lee	ERBITUX-PI Discussion Infusion Rate/Topical Seroids	1
12/11/2003	Email	To: Lee Pai Scherf From: Lily Lee	Schedule for Delivery of additional safety data for 0144	1
12/11/2003	Email	To: Lee Pai Scherf From: Lily Lee	Response to Request pertaining to recommendations in the proposed PI	1
12/11/2003	TCR	To: Pat Keegan From: L. Lee	Status of Requested Meeting	1
12/9 and 12/11/03	TCR	To: Chana Fuchs From: N. Mehta	BLA Review	1
12/11/2003	Amendment 009	To: G. Jones From: L. Lee	Process Validation Information as described in proposal given to FDA on November 14, 2003	1
12/12/2003	TCR	To: Sharon Sickafuse From: L. Lee	Confirm timing of discussion on BB36	1
12/12/2003	TCR	To: Chana Fuchs From: N. Mehta	BLA Review Update - Supplementary Process Validation submitted, Response to 483 sent out 12/12, not able to attend telecon 12/16, list of facility changes to be sent, Pre-meeting package to be sent, future discussions re:	1
12/12/2003	Letter	To: Wendy Weinburg, Marlene Swider, Chana Fuchs, Debbie Trout and Edwin Martinez From: N. Mehta	Form FDA 483 Responses to observations made during the PAI of BB36 manufacturing facility	1
12/12/2003	Email	To: Chana Fuchs From: N. Mehta	List of changes at the	1

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Date	Type	Addressee	Subject	Binder #
12/12/2003	Email	To: Sharon Sickafuse, Chana Fuchs and Pat Keegan From: L. Lee	Pre-Meeting document including background information needed for 12/23/03 CMC teleconference	1
12/15/2003	TCR	To: Chana Fuchs From: N. Mehta	BLA Review - Topics to be discussed in 12/16 telecon including ! assay, assay, Lot Release assays	1
12/15/2003	TCR	To: Debbie Trout From: N. Mehta	BLA Review Update - Supplementary Process Validation submitted, Response to 483 sent out 12/12, Lonza and Cardinal filing 483 responses by 12/19/03, amendment for MDL to be filed by 12/19/03	1
12/15/2003	Email	To: Lee Pai Scherf From: Lily Lee	Response to Request:	1
12/16/2003	Fax	To: Debbie Trout From: N. Mehta	Dye Intrusion Study Report	1
12/16/2003	TCR	To: Lily Lee From: Lee Pai Scherf	Request for additional paragraph in PI and FDA's Internal Preparation for 12/19/03 Telecon	1
12/17/2003	Email	To: L.Lee, J.Tarnowski, M.Needle, F.Fox, A.Daus, B.Hornberger, Q.Zhou, B.Saxena, Dan Lynch, M.Bloomstein, L.Yamashita, M. Birkhofer, S. Knapp, D.Smolin, C.Nicaise, O.Pfaff From: N. Mehta	Action Items from 12/16/03 telecon regarding US ! assay, Lot Release assays	1
12/18/2003	TCR	To: Nik Mehta From: S. Sickafuse	Comments Regarding Carton and Vial Labeling	1
12/22/2003	Amendment 010	To: G. Jones From: L. Lee	Data and recommendations section 8 (Clinical) for the proposed package insert language in response to FDA request for information	1
12/23/2003	Fax	To: Sharon Sickafuse From: L. Lee	List of attendess from 12/19/03 Teleconference	1
12/24/2003	Amendment 011	To: G. Jones From: L. Lee	CMC Information Including: 1) Protocol for testing and qualification of new Manufacturers Working Cell Banks, 2) Report on evaluation of container-closure, 3) Information on the use of MDL warehousing, 4) Updated results for on-going stability studies, 5) Confirmation that no new materials from Lonza would be released, 6) Overview of how IMClone/BMS will manage and monitor drug supply	1
12/24/2003	Email	To: Chana Fuchs From: N. Mehta	Response to question regarding the additional limit for IEF assay for stability	1
12/24/2003	Email	To: Chana Fuchs From: N. Mehta	Copy of BLA Amendment 011	1
12/29/2003	Amendment 012	To: G. Jones From: L. Lee	Revised Carton and Vial labels and Updated Lot Analysis Tables	1
12/31/2003	Email	To: C. Fuchs From: L. Lee	Responses to Questions relating to	1

* TCR- Telecontact Report

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Date	Type	Addressee	Subject	Binder #
1/2/2004	TCR	To: Nik Mehta From: S. Sickafuse	Revised Carton and Vial labels found to be acceptable	2
1/5/2004	Fax/Courier	To: Sharon Sickafuse From: N. Mehta	Change in ImClone Systems' address	2
1/5/2004	Email	To: Sharon Sickafuse From: L. Lee	Comments on Proposed PI	2
1/5/2004	Email	To: Chana Fuchs From: Nik Mehta	Comments on outstanding topics	2
1/5/2004	TCR	To: Nikhil Mehta From: Wendy Weinberg for Chana Fuchs	BLA Review -HACA, IEF Assay, Endotoxin lot release assay, HCP assay	2
1/6/2004	Email	To: Lee Pai-Scherf, Sharon Sickafuse From: L. Lee	Comments on FDA's changes on Proposed PI	2
1/6/2004	Email	To: Chana Fuchs From: Nik Mehta	Meeting minutes. Follow-up discussion regarding the use of BB36 manufactured Erbitux post approval	2
1/6/2004	TCR	To: Chana Fuchs From: Nikhil Mehta & Lily Lee	BLA Review - follow-up on items submitted, format of withdrawal letter and sBLA, Agreement to use BB36 material for clinical trials, Lonza review	2
1/7/2004	Email	To: Lee Pai-Scherf From: L. Lee	Information Request - Financial Disclosure	2
1/9/2004	TCR	To: Chana Fuchs Wendy Weinberg From: Nik Mehta	BLA review	2
1/9/2004	TCR	To: Nik Mehta From: S. Sickafuse	Review topics and Revised Vial and Carton Label	2
1/12/2004	TCR	To: Chana Fuchs, Wendy Weinberg From: Nik Mehta	BLA Review	2
1/12/2004	E-mail	To: Sharon Sickafuse From: Nik Mehta	Revised Vial and Carton Label	2
1/13/2004	TCR	To: Sharon Sickafuse From: Nik Mehta	Review topics and Revised Vial and Carton Label	2
1/14/2004	TCR	To: Sharon Sickafuse From: Nik Mehta	Revised Vial and Carton Label	2
1/14/2004	TCR	To: Nik Mehta From: Debbie Trout	Cardinal 483 Response	2
1/14/2004	Email	To: Sharon Sickafuse From: Lily Lee	Revised Vial and Carton Label	2
1/15/2004	Email	To: Sharon Sickafuse From: Lily Lee	Confirmation of reciept of revised PI	2
1/15/2004	Email	To: Chana Fuchs From: Nik Mehta	(No Subject Listed in E-Mail) Reference Standard material and release specs	2
1/16/2004	Amendment 013	To: Glen Jones From: L. Lee	Revised Vial and Carton Labels, Revised Proposed Package Insert, Response to Questions on HACA Assay, Additional Financial Disclosure Information, Change of Address Notification	2
1/20/2004	Fax	To: Lily Lee From: Sharon Sickafuse	Clinical Phase 4 Commitments for Cetuximab BLA	2

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Date	Type	Addressee	Subject	Binder #
1/21/2004	E-mail	To: Lily Lee From: Lee Pai Scherf	Revised Package Insert: Version Jan. 14	2
1/21/2004	E-mail	To: Sharon Sickafuse From: Lily Lee	Response to List of Clinical Phase 4 Commitments & Milestones for Commitment 5 (Pediatric Studies)	2
1/21/2004	TCR	To: Nikhil Mehta From: Wendy Weinberg	BLA Review, Shipping conditions for drug substance from	2
1/21/2004- 1/22/2004	TCR	To: Nikhil Mehta From: Marlene Swider	BLA Review, Status of Review of the Cardinal 483 Response	2
1/21/2004- 1/22/2004	TCR	To: Nikhil Mehta From: Chana Fuchs	BLA Review, Withdrawal of BB36, BLA CMC Amendment,	2
1/22/2004	Email	To: Chana Fuchs From: Nikhil Mehta	Information requested to date (final amendment)	2
1/23/2004	Email	To: Chana Fuchs and Wendy Weinberg From: Nikhil Mehta	Responses to s Questions (3:07pm)	2
1/23/2004	Email	To: Chana Fuchs From: Nikhil Mehta	5015 483 #2 update 2004- pm)	2
1/23/2004	Email	To: Chana Fuchs From: Nikhil Mehta	Registration Numbers (6:46pm)	2
1/23/2004	TCR	To: Chana Fuchs From: Nikhil Mehta, Lily Lee, & Joe Tarnowski	BLA Review: to discuss recent question from Wendy Weinberg regarding the availability of additional process validation results for	2
1/23/2004	TCR	To: Nikhil Mehta From: Sharon Sickafuse	Review topics and Revised Vial and Carton Label	2
1/26/2004	TCR	To: Lily Lee From: Chana Fuchs	Withdrawal of BB 36	2
1/26/2004	Email	To: Sharon Sickafuse Chana Fuchs From: Lily Lee	Letter withdrawing BB36	2
1/27/2004	Email	To: Sharon Sickafuse From: Lily Lee	Finalization of PI - 1/27/04 changes okayed	2
1/27/2004	Amendment 014	To: Glen Jones From: L. Lee	Withdrawal of BB36, Timeline for Clinical phase 4 Commitments, Letter Requesting Accelerated Approval	2
1/28/2004	Letter	To: Sharon Sickafuse From: Nikhil Mehta	Proposed Carton & Vial Labels	2
1/28/2004	Email	To: Chana Fuchs From: Nikhil Mehta	Resin and TFF re-use	2
1/28/2004	Email	To: Sharon Sickafuse From: Nikhil Mehta	Tracking Number for Delivery, Thurs. Jan 29, 2004	2
1/28/2004	Email	To: Chana Fuchs, Wendy Weinberg From: Nikhil Mehta	Responses to questions from	2
1/28/2004	Email	To: Chana Fuchs, Wendy Weinberg From: Nikhil Mehta	Responses to questions from	2
1/29/2004	E-mail	To: Sharon Sickafuse, Pat Keegan From: Lily Lee	RE: PI? (Package Insert Correspondence)	2
1/29/2004	Email	To: Sharon Sickafuse From: Nikhil Mehta	Revised Vial and Carton Labels without latest comments	2
1/30/2004	Email	To: Sharon Sickafuse From: Nikhil Mehta	Revised Vial and Carton Labels with latest comments incorporated	2

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Date	Type	Addressee	Subject	Binder #
1/30/2004	Email	To: Sharon Sickafuse From: Nikhil Mehta	Revised Vial and Carton Labels with today's latest comments added	2
1/30/2004	Email	To: Chana Fuchs, Wendy Weinberg From: Nikhil Mehta	Updated Resin/Membrane Reuse Document	2
1/30/2004	Email	To: Sharon Sickafuse From: Nikhil Mehta	100 mg (2 mg/mL) on the carton has been bolded	2
2/2/2004	Email	To: Sharon Sickafuse From: Lily Lee	"FDA has no further comments" and plan to include latest vial and carton in 2/3/04 amendment	2
2/2/2004	Email	To: Sharon Sickafuse From: Lily Lee	Final Draft PI reflecting changes as communicated on January 30, 2004.	2
2/2/2004	Email	To: Sharon Sickafuse From: Lily Lee	Plan to send PI either in 2/3/04 amendment or final amendment	2
2/3/2004	Amendment 015	To: Glen Jones From: L. Lee	Revised Final Vial and Carton Labels, Responses to CMC review questions	2
2/3/2004	Fax	To: Lily Lee From: Sharon Sickafuse	Product PMCS - CMC Post Marketing Commitments	2
2/5/2004	Fax	To: Sharon Sickafuse From: Lily Lee	Revised Post Approval Clinical Commitments	2
2/5/2004	Email	To: Chana Fuchs; Sharon Sickafuse From: Nikhil Mehta	Post Marketing CMC Commitments	2
2/6/2004	Amendment 016	To: Glen Jones From: L. Lee	Final Draft PI, Post Marketing Commitments	2
2/12/2004	Letter	To: Lily Lee From: Sharon Sickafuse	Approval Letter - License for ImClone Systems to Manufacture Cetuximab	2
2/12/2004	Letter	To: Glen Jones From: L. Lee	Manufacturing Supplement to BLA	2
2/18/2004	Letter	To: FDA (Central Document Room, CDER) From: L. Lee	15-Day Alert Report - Mfg. Control #12502589/0	2
2/23/2004	Letter	To: Lily Lee From: Karen D. Weiss	Approval Letter - License for ImClone Systems to Manufacture Cetuximab with an Enlcosure on Labeling	2
2/24/2004	Letter	To: Glen Jones From: L. Lee	Notification that regulatory reporting responsibilities for U.S. drug safety would be transferrred to BMS	2
2/25/2004	TCR	To: S.Sickafuse From: Debbie Lynch	To alert CBER to the IND and BLA submissions transferring regulatory reporting responsibilities for drug safety in the U.S. to BMS	2
3/1/2004	Letter	To: FDA (Central Document Room, CDER) From: Debbie Lynch for L. Lee	15-Day Alert Report - Mfg. Control #12508859	2

* TCR- Telecontact Report

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

POWER OF ATTORNEY CONCERNING APPLICATION FOR PATENT TERM EXTENSION

I, Thomas C. Gallagher, Vice President, Intellectual Property of ImClone Systems Incorporated, the undersigned agent for ImClone Systems Incorporated, hereby appoints Deborah A. Somerville, Registration No. 31,995 of

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New York, NY 10004

as the attorney, as well as the registered practitioners of Kenyon & Kenyon included in the Customer Numbers (23838 and 26646) to act on its behalf before the U.S. Patent and Trademark Office and to receive all communications and notices relative thereto in connection with the application for patent term extension concerning the below identified patent.

TITLE OF INVENTION	:	Monoclonal Antibodies Specific to Human Epidermal Growth Factor Receptor and Therapeutic Methods Employing Same
PATENT NUMBER	:	6,217,866
FILING DATE	:	June 7, 1995
ISSUE DATE	:	April 17, 2001
INVENTORS	:	Schlessinger, et al.
APPLICANT'S AGENT	:	ImClone Systems Incorporated
ADDRESS	:	180 Varick Street New York, New York 10014

DATE: 4/7/04 SIGNATURE: _____

Name: Thomas C. Gallagher, Reg. No. 37,066
Title: Vice President, Intellectual Property
ImClone Systems Incorporated